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# Structural and neurochemical alterations in unipolar and bipolar major depression

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# STRUCTURAL AND NEUROCHEMICAL ALTERATIONS IN UNIPOLAR AND BIPOLAR MAJOR DEPRESSION

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# Abstract

Depressive disorders are common and debilitating conditions; however, current methods of diagnosis and treatment are suboptimal, largely due to a lack of understanding of the biological basis of these disorders. Neuroimaging has provided substantial insights in this area, but one particularly understudied area is the relationship between unipolar and bipolar depression. These disorders have similar symptom profiles but require different treatment strategies, making their diagnosis and management challenging for clinicians.

The overarching aim of this thesis is to understand differences and similarities in the structure and neurochemistry of neurobiological systems underlying unipolar and bipolar depression. This question is addressed in three ways: Firstly meta-analyses of structural neuroimaging studies looking at alterations in grey and white matter were performed to identify patterns of changes that were common or specific to either disorder. Secondly, an original investigation was carried out to identify patterns of neurochemical alteration that differ between unmedicated patients with unipolar and bipolar depression. Lastly, the appropriateness of a dimensional approach to bipolarity in depression was evaluated by looking for structural neural correlates of bipolar symptoms within patients with unipolar and bipolar depression.

The results of these studies show that although many neurobiological alterations are common to unipolar and bipolar depression, there are changes in grey matter volume that are specific to unipolar depression, and changes in white matter volume that are specific to bipolar depression. However, alterations in grey matter volume do not correlate with bipolarity when treated as a dimensional characteristic. These results contribute to our understanding of structural and neurochemical alterations in

depressive disorders, and provide targets for future research into improved diagnosis of these conditions.

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# 1 Introduction

## 1.1 Unipolar and bipolar affective disorders

Major unipolar and bipolar affective disorders are mental health problems with significant impact on quality of life and high societal personal and economic costs (Üstün, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004). Both disorders are relatively common, with lifetime prevalence of 18% and 2% respectively (Kessler et al., 2003; Merikangas et al., 2007). A primary symptom of both conditions is a depressive state, where individuals experience a range of symptoms including low mood, loss of energy and interest for pleasurable activities, negative cognitions, numerous biological features (e.g. disrupted sleep and appetite), and suicidal ideation and behaviours in more severe cases. Bipolar disorder is further characterised by episodes of mania or hypomania, where individuals experience numerous symptoms that include elevated mood and energy, decreased need for sleep, and a tendency to engage in risky behaviours. Psychotic features such as delusions and hallucinations can occur in more severe presentations, and these often require hospitalisation. Bipolar disorder has been further divided into subtypes, most prominently type I and II, which is a clinical distinction based on the presence of manic (type I) or less severe hypomanic episodes (type II).

Despite the obvious burden these illnesses place on the individual and society, clinical outcomes are often far from desirable. In unipolar major depression, a significant number of sufferers do not respond or partially respond to their first treatment, either with antidepressant medication or psychological therapy, and approximately one third do not respond to any treatment (Rush et al., 2006). Of those who do recover, 35% experience further episodes (Eaton et al., 2008). Similarly, in bipolar depression over a third of patients do not respond to the available treatments, and around half of those

who do will nonetheless experience further episodes (Perlis et al., 2006). Together, failures to respond, optimise and maintain treatment can result in prolonged and recurrent illnesses, further increasing the burden of illness.

## 1.2 Depressive state as research focus in unipolar and bipolar disorders

Despite the poor efficacy of current available treatments, our limited understanding of the mechanisms underlying these conditions hampers the development of new treatments. It follows that improving our understanding of the neurobiological substrates of affective disorders is crucially important to facilitate biomedical progress in the field of mood disorders.

An approach that could facilitate our understanding of the biology of mood dysregulation is to focus on depression as the mood state experienced by both unipolar and bipolar disorders. This could aid in elucidating common and distinct patterns of biological abnormalities that may guide the development of more targeted novel therapeutics. Additionally, given recent initiatives to look beyond traditional diagnostic boundaries and instead focus on dimensional aspects of symptomatology (Insel et al., 2010), a better understanding of the biological substrates of these conditions could improve our diagnostic systems and our understanding of the relationship between unipolar and bipolar depression.

A further clinical advantage of this research focus is based on the observation that depressive symptoms can be the initial presentation of unrecognised bipolar disorder leading to a delay in accurate diagnosis and effective clinical management resulting in poorer treatment responses (Hirschfeld, Lewis, & Vornik, 2003). It is in fact not uncommon that individuals suffering with bipolar disorder (especially type II) present

to clinical services when experiencing depressive symptoms, making it clinically challenging to determine whether a bipolar diagnosis may be appropriate (Mitchell, Goodwin, Johnson, & Hirschfeld, 2008). The main reason is the retrospective evaluation of the bipolar symptoms which have already occurred. In case of first presentations, detailed diagnostic evaluations are often necessary to optimise the chance of a correct diagnosis and minimise the risk of misdiagnosing bipolar depression as unipolar major depression (Hirschfeld et al., 2003). Misdiagnosis results in patients being treated with antidepressant medications, not considered the treatment of choice in bipolar depression, potentially contributing to treatment refractoriness and mood cycle acceleration (e.g. switching to hypomanic or manic symptoms) (Patel et al., 2015; Sachs et al., 2007; Sidor & Macqueen, 2011). The ability to discriminate biologically between unipolar from bipolar at the time of the first presentation, especially when depressive symptoms are the leading clinical syndrome, might improve diagnosis and ultimately clinical outcome in mood disorders (Leuchter et al., 2010).

The development of imaging technology has made the brain a major target for neurological based biological research, and over the past two decades a growing body of evidence has suggested that both major depression and bipolar disorder are associated with substantial structural, functional, and neurochemical alterations in the brain (Kempton, Geddes, Ettinger, Williams, & Grasby, 2008; M. J. Taylor, 2014a; Wise, Cleare, Herane, Young, & Arnone, 2014). Here I will focus on describing structural and neurochemical changes in these disorders, and their potential utility in differentiating unipolar and bipolar depression. While functional neuroimaging has provided valuable insights into the neural processes underlying these conditions, heterogeneity in the methods and the variability of the tasks used limit comparisons

between disorders. Methods used to measure structural and neurochemical differences are otherwise relatively consistent and are detailed below.

## 1.3 Methods for assessing structural and neurochemical alterations

### *1.3.1 Structural neuroimaging*

Studies of brain structure in psychiatric disorders have benefitted greatly from the development of magnetic resonance imaging (MRI), along with increasingly sensitive methods of analysing the data it produces. The two most common analysis methods used in the literature are voxel-based methods and volumetric methods. Voxel-based techniques such as voxel-based morphometry (Ashburner & Friston, 2000) allow quantification of grey and white matter volume or density changes with high spatial resolution by performing statistical analyses independently on each voxel of a structural image that has been spatially normalised to a standard template. This method can provide an estimate of grey matter volume differences between groups across the whole brain, without necessarily requiring the identification of specific regions, making it relatively unbiased. However, the mass-univariate analysis methods typically used to assess statistical differences between groups require substantial multiple comparisons correction, which often makes them less sensitive to less substantial grey matter changes.

In contrast, volumetric methods use either manual or automatic segmentation techniques (Fischl, 2012; Tae, Kim, Lee, Nam, & Kim, 2008) to identify specific brain regions based on anatomical boundaries and quantify their volume as a whole. These methods have been widely used to assess the volume of brain areas of interest (Arnone, McIntosh, Ebmeier, Munafò, & Anderson, 2012; Kempton et al., 2008), such as the

hippocampus and amygdala, and have been shown to be more sensitive to volumetric alterations in the hippocampus than voxel-based morphometry (Bergouignan et al., 2009). However, these methods do not allow accurate localisation of regions of volume alteration due to their quantification of relatively large brain regions as a whole.

In addition to studying the volume of white matter using the techniques described above, more recently developed methods have allowed the assessment of white matter microstructure to determine its integrity. Diffusion tensor imaging (DTI) has allowed the measurement of differences in white matter microstructure in major depression more precisely by investigating the diffusion of water molecules within white matter tracts (Le Bihan et al., 2001). This is based on the tendency of water molecules to diffuse along the path of least resistance, which leads water molecules within axons to diffuse along the axon. By tracking their movement, the location of white matter tracts can therefore be identified. Additionally, by assessing the direction of their movement the integrity of these tracts can be investigated. For example, the most commonly used measure of integrity, fractional anisotropy (FA), measures the isotropy of water diffusion at a given voxel. Given that diffusion within a white matter tract will tend to be anisotropic, moving in alignment with the direction of the tract, any decrease in anisotropy implies that there may be a loss of integrity in the tract, allowing water molecules to diffuse outside of it (Basser & Pierpaoli, 1996). Other measures, such as radial and axial diffusivity (Song et al., 2002, 2005), provide complementary information about white matter microstructure, but these are reported less frequently in the literature than fractional anisotropy.

DTI data can be analysed in either a tract-based or a voxel-based manner. Tract-based methods identify an entire white matter tract and describe characteristics, such as FA,

of the entire pathway (Müller et al., 2009). This method is sensitive to global changes in integrity across an entire tract of interest, but does not allow the identification of specific locations with a tract that may be affected. In contrast, voxel-based methods (such as voxel-based analysis or tract-based spatial statistics) work in a similar way to voxel-based morphometry and allow quantification of white matter integrity at the level of individual voxels (S. M. Smith et al., 2006). This enables specific areas of white matter alterations that may involve multiple tracts to be identified with relatively high spatial resolution. However, this some variants of this approach are susceptible to distortions caused by normalisation of diffusion images to a standardised template (S. M. Smith et al., 2006).

### *1.3.2 Neurochemical neuroimaging*

Neurochemistry in affective disorders has been extensively studied with two main techniques: positron emission tomography (PET) and magnetic resonance spectroscopy (MRS). In PET, molecules of interest, such as ligands for a particular receptor, are radiolabelled with radionuclides allowing their location to be traced from the emission of photons. This allows spatially accurate mapping of neurotransmitters and their receptors *in-vivo,* and has therefore been of great interest in psychiatry. Salient examples of the utility of PET in psychiatry and neurology are the ability to track presynaptic dopamine production using [18-F]FDOPA, radiolabelled L-DOPA (Brooks et al., 1990; Ernst, Zametkin, Matochik, Jons, & Cohen, 1998), and assessing 5-HT1A receptor levels using [11-C]WAY-100635 (Sargent et al., 2000), a radiolabelled 5-HT1A antagonist. However, despite the clear benefits of this method, it does have a number of limitations. For example, difficulties in reference locations used to quantify the relative level of ligands in a region of interest have led to

inconsistent findings (Shrestha et al., 2012), and the cost and practical difficulties involved in PET imaging make studies with large samples challenging.

In contrast, MRS uses magnetic resonance to assess the levels of various neurotransmitters and neurometabolites based on the resonant properties of hydrogen nuclei in a magnetic field, where differences in the chemical makeup of compounds lead to different resonance frequencies allowing them to be differentiated. MRS allows simple and inexpensive quantification of many neurometabolites of interest, including putative markers of neuronal health such as N-acetyleaspartate and myo-inositol; however the range of neurotransmitters that it can assess is limited. While glutamate is typically detectable at 3 Tesla (Schubert, Gallinat, Seifert, & Rinneberg, 2004a), accurate detection of GABA typically requires specially designed acquisition sequences (Puts & Edden, 2012), and other neurotransmitters such as serotonin and dopamine are not present in sufficient quantities to be detected with MRS. A further substantial limitation of MRS is its poor spatial resolution, as it requires signal to be acquired from a single large voxel and therefore does not allow metabolites to be easily mapped in space. Newer developments in MRI, such as GluCEST (Davis et al., 2015), have begun to allow non-invasive spatial mapping of glutamate in vivo, but have yet to be used in affective disorders. Although these methods allow quantification of a range of metabolites, here I will focus on the insights they have provided into abnormality in neurotransmitter systems in affective disorders.

## 1.4 Structural and neurochemical changes in unipolar major depression

### *1.4.1 Volumetric and grey matter changes in unipolar major depression*

There is substantial evidence of brain morphometric changes observed with structural Magnetic Resonance Imaging (sMRI) in unipolar major depression in both cortical and

subcortical regions. Volumetric reductions in cortical structures have been described in the ventromedial prefrontal cortex, such as the orbitofrontal cortex, ventromedial prefrontal cortex and anterior cingulate cortex (Abe et al., 2010; K. N. Botteron, Raichle, Drevets, Heath, & Todd, 2002; Salvadore et al., 2011; van Tol et al., 2010), as well as lateral prefrontal systems including areas within the ventrolateral and dorsolateral prefrontal networks (Salvadore et al., 2011; Serra-Blasco et al., 2013; van Tol et al., 2010). Although some inconsistency in these findings does exist in the literature (Soriano-Mas et al., 2011; Zou et al., 2010), meta-analytic summary effect sizes generally support the notion of prefrontal morphometric reduction and grey matter loss in these regions in major unipolar depression (Arnone et al., 2016; Selvaraj et al., 2012). The most commonly reported subcortical brain regions were morphometric abnormalities have been demonstrated include the ventral striatum (Kim, Hamilton, & Gotlib, 2008; C. Ma et al., 2012), the hippocampus and parahippocampal gyrus (Bremner et al., 2000; Sheline, Gado, & Kraemer, 2003), and the amygdala (Frodl, Meisenzahl, Zetzsche, et al., 2004). Whilst volumetric reduction in the hippocampus remains to date the most replicated finding in major unipolar depression (Kempton et al., 2011), volumetric changes in the amygdala, a region known to be involved in affective processing, are less consistent (Arnone, McIntosh, et al., 2012). It has been suggested that incongruences in the findings in the amygdala might be explained by variability in clinical characteristics of the included patients. For instance, Bora and others found evidence of amygdala morphometric reduction in major depression only in a subset of patients with anxiety disorders comorbid to major depression (Bora, Fornito, Pantelis, & Yücel, 2012). Besides clinical differences there are a range of other confounders which might introduce sufficient variance in the samples of studies potentially amplifying or dampening differences in findings in volumetric differences. Examples include genetic variants in the brain-derived

neurotrophic factor and serotonin transporter genes shown to significantly affect the volume of the hippocampus in depression (Frodl et al., 2007; Frodl, Meisenzahl, Zill, et al., 2004) and the effect of stressful life events and stress hormones on grey matter volumes in depression (Treadway et al., 2009; Vythilingam et al., 2002). Furthermore, successful response to pharmacological treatment has been shown to affect grey matter volume in key regions involved in depression (Arnone et al., 2013), suggesting a plastic role of targeted interventions on brain structure that could explain heterogeneity in results. Finally, there are some indications that there may be state effects on brain morphology in depression. For example, hippocampal volume has been shown to be selectively reduced in currently depressed patients while in remitted patients it is comparable to controls (Arnone et al., 2013), and similar patterns have been shown in a number of prefrontal areas (Salvadore et al., 2011).

Post-mortem studies suggests that the neuropathology underlying the volumetric reduction observed in the hippocampus with sMRI is attributable to an increase in both neuronal and glial density coupled with a reduction in the soma size of pyramidal neurons (Stockmeier et al., 2004). In the anterior cingulate cortex, a reduction in dendritic branching has been observed (Hercher, Canetti, Turecki, & Mechawar, 2010) suggesting that deterioration in connectivity between neurons might be responsible for reductions in overall volume. It has also been suggested that the shortened telomere length demonstrated in individuals with major depression might contribute to an accelerated cell ageing process in the hippocampus resulting in volumetric loss (Mamdani et al., 2015). Another observation has indicated that hippocampal grey matter volume reductions might be the result of neuroinflammation, potentially mediated by altered levels of neuroprotective and neurotoxic kynurenine pathway metabolites (Savitz et al., 2015).

### *1.4.2 White matter changes in unipolar major depression*

White matter changes in major depression have been noted in the area of the corpus callosum when investigated with computerised tomography and MRI techniques, largely supporting a reduction in surface area (Kemp et al., 2013; Walterfang et al., 2009). However a number of studies have failed to find such an effect (Lacerda et al., 2005; Lammers et al., 1991; Ozalay et al., 2013), and the field has benefited from more recent developments in MRI techniques that allow the measurement of white matter integrity as opposed to simple area, including the introduction of DTI. Many studies have reported reduced FA, a measure of white matter integrity, in a number of pathways including the superior longitudinal fasciculus (Wu et al., 2011; Zou et al., 2008) and genu of the corpus callosum (Wen-bin Guo, Liu, Chen, et al., 2012; Murphy et al., 2012), although there are some inconsistences in the findings (Choi et al., 2014; Korgaonkar et al., 2011), likely due to differences in sample characteristics and methods of analysis. The decrease in FA measured in the uncinate fasciculus (W. D. Taylor, MacFall, Gerig, & Krishnan, 2007; Zhang et al., 2012), the white matter tract connecting fronto-limbic regions, is particularly compelling given the importance of these regions in depression as evidenced by sMRI studies.

Post-mortem studies suggest that demyelination (as indicated by myelin staining methods) (Regenold et al., 2007), might contribute to explaining the neuropathology of white matter abnormalities in major depression, together with the possible contribution of white matter lesions (which are often associated with demyelination) demonstrated with sMRI (Arnone, McIntosh, et al., 2012). Another advantage of DTI studies is the possibility to take advantage of other measures of white matter integrity besides FA. Two recent studies that measured radial diffusivity (RD), a measure typically increased in the presence of demyelination, have suggested the presence of

demyelination (increased RD) in major depression in areas where a concomitant reduction of FA was detected (Korgaonkar et al., 2011; Murphy et al., 2012).

### *1.4.3 Neurochemical alterations in unipolar major depression*

Neurochemical abnormalities have also been frequently detected in major depression. Positron emission tomography (PET) has been used to measure serotonin 1A (5-HT1A) receptor binding with the aim of understanding the nature of alterations in serotonergic neurotransmission in major depression. However, findings from these studies are contradictory, with both increases and decreases in 5-HT1A receptor binding reported in MDD (Drevets et al., 2007). As noted by a recent review (Shrestha et al., 2012), the inconsistency in findings is likely to be due to methodological differences and the field would benefit from gaining a better understanding of how different analysis methods can produce such contrasting results. The most important difference between studies is the choice of reference tissue, which is used to normalize radioligand binding in the region of interest. Results can vary greatly depending on the choice of reference, and there is no agreement on which is the optimal method (please see Shrestha et al. (2012) for a detailed review of this and further issues in these studies). Findings in PET studies of other neurotransmitter systems are also mixed. A number of studies have investigated various aspects of the dopamine system, finding reduced dopamine transporter binding in the striatum, indicative of reduced levels of dopamine, (Meyer et al., 2001) and reduced D1 receptor density in the left caudate (Cannon et al., 2009). However there have also been null findings, for example one study found no difference in D2 receptor availability in the striatum or thalamus (Hirvonen et al., 2008). Nonetheless, despite the inconsistencies in these studies the evidence does suggest that serotonergic and dopaminergic neurotransmission may be affected in major depression.

Magnetic resonance spectroscopy (MRS) has also been applied to examine changes in glutamatergic neurotransmission, and the majority of studies have found major depression to be associated with reduced levels of glutamate and glutamine, particularly in the prefrontal cortex (Arnone, Mumuni, Jauhar, & Cavanagh, 2015; M. J. Taylor, 2014a). The cellular mechanism underlying this reduction in glutamate levels is unclear, although it has been suggested that this may be a reflection of altered glial function (Arnone, Mumuni, Jauhar, & Cavanagh, 2015). Similarly, MRS research has found gamma-amino butyric acid (GABA) levels to be reduced in the prefrontal cortex of patients with major depression (Hasler et al., 2007), suggesting that depression may be associated with abnormalities in inhibitory neurotransmission.

Similar results have been shown in the occipital cortex (Sanacora et al., 2004), a region that is typically not functionally implicated in depression, suggesting that these reductions may be global effects rather than being specific to systems associated with affective symptoms. However it should be noted that there are some null results in the occipital cortex, and one study found that treatment with antidepressant medication does not affect GABA or glutamate levels (Godlewska, Near, & Cowen, 2014). Notably, GABA concentrations appear to be comparable with control subjects in remitted depression (Hasler et al., 2005) indicating that GABAergic reductions may be specific to the depressive state.

Some studies have also investigated n-acetyl-L-aspartate (NAA), a marker of neuronal integrity, in major depression, and shown that levels are reduced in prefrontal white matter (Zhong et al., 2014) and the putamen (Vythilingam et al., 2003), but two studies have failed to find such an effect in the anterior cingulate cortex (Auer et al., 2000; Zhong et al., 2014). There is also some evidence of reduced myo-inositol, a marker of glial health, in the prefrontal cortex of patients with major depression

(Coupland et al., 2005), although another study failed to find this (Auer et al., 2000). Together, these studies suggest widespread alterations in glutamatergic and GABAergic neurotransmission in unipolar depression, as well as reductions in neuronal integrity.

## 1.5 Structural and neurochemical changes in bipolar disorder

### *1.5.1 Volumetric and grey matter changes in bipolar disorder*

Many studies have used structural MRI to evaluate grey matter volume changes in bipolar disorder. One of the most consistent findings is that individuals with bipolar disorder show grey matter reductions in lateral and medial prefrontal areas (Ha, Ha, Kim, & Choi, 2009; Stanfield et al., 2009). Findings in subcortical structures have been less consistent. Many studies have failed to find hippocampal volume reduction in bipolar disorder (Kempton et al., 2008), unlike major depression, although this is not always the case (Hajek, Cullis, et al., 2012). This variation in findings might be due to medication differences between samples. A recent meta-analysis found reduced hippocampal volumes only in studies using patients with low lithium load, suggesting that reduced hippocampal volume in bipolar disorder is ameliorated by lithium treatment (Hajek, Kopecek, Hoschl, & Alda, 2012). Taken together, these findings indicate that BD is associated with widespread volumetric differences, although these are clearly affected by medication.

The available evidence suggests that the basis of these volumetric changes may be similar to major depression, although research in this area is sparser in bipolar disorder. Studies have identified reduced levels of glial fibrillary acidic protein mRNA, indicative of reduced astrocyte density, in post-mortem brain tissue from individuals

with bipolar disorder (Webster, O'Grady, Kleinman, & Weickert, 2005) suggesting that glial pathology may be partially responsible for volumetric reductions. However a number of studies have also reported reductions in both neuronal density and size in several areas, including both prefrontal and subcortical regions (Gigante et al., 2011), indicating that neuronal pathology may also underlie volumetric alterations. As with major depression, increased levels of inflammatory markers have been found in post-mortem samples of prefrontal tissue from patients with bipolar disorder (J. S. Rao, Harry, Rapoport, & Kim, 2010), while variation in the interleukin-1 gene has been associated with grey matter changes in bipolar disorder, as measured using MRI (Papiol et al., 2008). As with major depression, this provides evidence for a potential role of inflammatory processes in the grey matter volume reduction observed in bipolar disorder.

### *1.5.2 White matter changes in bipolar disorder*

With regard to white matter, studies have consistently found reduced corpus callosum area in BD compared with healthy controls (Arnone, McIntosh, Chandra, & Ebmeier, 2008). This is in contrasts to studies in MDD that have failed to consistently find such a reduction (Arnone, McIntosh, et al., 2012). BD is also associated with white matter microstructural alterations, as shown by numerous studies using DTI (Benedetti, Absinta, et al., 2011; Chaddock et al., 2009). Affected areas include the corpus callosum, superior longitudinal fasciculus, inferior longitudinal fasciculus suggesting that white matter abnormalities may contribute to the pathogenesis of the disorder. However as in MDD studies, findings vary from study to study and it will be important for future research to elucidate the basis of this heterogeneity in results. As with major depression, decreases in white matter integrity may be due to demyelination, as

suggested by both post-mortem studies (Regenold et al., 2007) and DTI studies measuring radial diffusivity (Benedetti, Absinta, et al., 2011).

### *1.5.3 Neurochemical alterations in bipolar disorder*

With regard to neurochemical changes, a number of abnormalities have been identified. Like those in major depression, studies using PET to examine serotonergic neurotransmission in bipolar disorder have found mixed results. While some research has found increased radioligand binding to the serotonin transporter in prefrontal and subcortical regions (Cannon et al., 2006), likely representing increased transporter density, others have found an opposing pattern of results (Oquendo et al., 2007) making it difficult to draw reliable conclusions on the nature of serotonergic alterations in the condition. A limited number of studies have examined dopaminergic neurotransmission in bipolar disorder. One study found reduced D1 receptor binding in the prefrontal cortex in a small sample of patients (Suhara et al., 1992). Another study showed increased D2 receptor binding, however this appeared to be restricted to patients with psychotic symptoms indicating that this effect may be more strongly related to symptoms of psychosis than affective symptoms (Pearlson et al., 1995).

MRS studies examining levels of glutamate in bipolar disorder have tended to find the opposite pattern to those in major depression, with increased prefrontal glutamate and glutamine being a common finding (M. J. Taylor, 2014a). Findings of studies focusing on GABA levels using MRS are more mixed, with some research finding reduced levels of GABA in occipital regions (Bhagwagar et al., 2007), and others finding increased GABA concentrations (Brady et al., 2013), while one study failed to find any difference between patients with bipolar disorder and controls (Kaufman et al., 2009). Numerous studies have also identified reductions in NAA in the prefrontal cortex and subcortical structures (Yildiz-Yesiloglu & Ankerst, 2006), and there is some indication that levels

of NAA are inversely correlated with the number of manic episodes (Frye et al., 2007), suggesting that repeated mania may cause a reduction in neuronal integrity. There is also evidence of a reduction in myo-inositol in frontal and temporal cortex (Silverstone, McGrath, & Kim, 2005), with some indications that this is normalised with lithium pharmacotherapy (Machado-Vieira et al., 2015). Together this research indicates the presence of abnormalities in major neurotransmitter systems and a reduction in neuronal integrity, although the evidence is more limited in quantity and consistency than in major depression.

## 1.6 Comparisons between major depression and bipolar disorder

### *1.6.1 Structural findings*

The evidence described thus far demonstrates that major depression and bipolar disorder appear to share largely similar neurobiological substrates, with both showing alterations in circuits involved in emotion processing and regulation. However, some important differences between conditions have been observed, which suggests that these disorders may be associated with distinct neurobiological pathology, and that neuroimaging based markers may be able to distinguish between the two.

Perhaps the most notable difference observed in structural neuroimaging studies is in the hippocampus. Here studies in major depression typically see reduced volume, while those in bipolar disorder find no differences relative to controls (Kempton et al., 2011). However, as noted above, there have been suggestions that this may be due to neuroprotective effects of lithium treatment in bipolar disorder (Hajek, Cullis, et al., 2012; Hajek, Kopecek, et al., 2012). This suggests that differences between conditions in the hippocampus may represent an effect of medication as opposed to a disease-

related process. In addition, studies in major depression have indicated that hippocampal volume reduction may only be present in patients with recurrent illness (Schmaal et al., 2015), indicating that this may not be a reliable point of difference in first episode patients.

Outside the hippocampus, volumetric analyses of specific regions have identified few regions showing substantial differences between disorders (Kempton et al., 2011), and there is a paucity of comparisons between disorders using techniques that are more sensitive to localised grey matter alterations, such as voxel-based morphometry. One recent study using this technique in a large sample of individuals with bipolar and unipolar depression identified grey matter volume reductions in the anterior cingulate cortex as being specific to unipolar depression (Redlich et al., 2014). One further study using unmedicated patients with unipolar and bipolar depression found reduced cortical thickness in bipolar relative to bipolar patients in the dorsolateral prefrontal and parietal cortices (Lan et al., 2014). This suggests that volumetric alterations in other regions may also differentiate the conditions, although this study did not look at subcortical morphometric differences. However, given the lack of research in this area it is unclear whether these results will be replicable, and whether there may be further structural differences between conditions that might shed light on distinct neural mechanisms.

With regard to white matter, there have again been relatively few studies directly comparing the two conditions, and it is difficult to identify consistent patterns of difference. Corpus callosum area appears to be reduced in bipolar disorder, while it is comparable with healthy controls in major depression (Kempton et al., 2011) suggesting that pathology in this region may be specific to bipolar disorder. In addition, Redlich et al. (2014) found reduced white matter volume in the cerebellum

and hippocampus in individuals with bipolar disorder relative to those with major depression, suggesting that there may be more widespread differences in white matter volume between disorders. Furthermore, one DTI study comparing the two disorders found reduced integrity of the superior longitudinal fasciculus in bipolar depression compared with unipolar depression (Versace et al., 2010a) indicating that the two disorders may be associated with distinct patterns of alteration in white matter integrity.

### *1.6.2 Neurochemical findings*

Research into neurochemical abnormalities in affective disorders may also provide insights into common and distinct pathways underlying major depression and bipolar disorder. The PET literature is less promising due to the substantial inconsistencies in results, even within each condition. Additionally, only one study has compared neurotransmitter function between unipolar and bipolar depression using PET, finding increased 5-HT transporter levels in unipolar depression in the periaqueductal grey, and the opposite pattern in the raphe nuclei.

However studies assessing glutamate levels using MRS have provided exciting results that hint at a potential distinction in glutamatergic function between these disorders. MRS studies in bipolar disorder have typically found that glutamate levels in prefrontal regions, particularly the anterior cingulate cortex, are increased relative to controls, in contrast to the reductions seen in major depression (Arnone, Mumuni, Jauhar, & Cavanagh, 2015; Chitty, Lagopoulos, Lee, Hickie, & Hermens, 2013; M. J. Taylor, 2014a). This indicates that divergent glutamatergic pathologies may characterise the two disorders, however there are to date no direct comparisons of glutamate levels in unipolar and bipolar depression, which could provide a more accurate view of distinct alterations in glutamatergic neurotransmission.

This pattern of results is of particular interesting because if the direction of glutamatergic alterations is truly divergent in these two disorders this could provide a clinically useful diagnostic biomarker. However, this does raise a further question. Ketamine has been demonstrated to have rapid antidepressant effects in both unipolar and bipolar depression. Given that ketamine increases glutamate levels, as measured using MRS, in the anterior cingulate cortex, it is unclear how it is effective in the treatment of bipolar disorder if this condition is associated with elevated glutamate levels in this region. It is possible however that these apparently contradictory results arise from differences in the specific regions of the anterior cingulate cortex under investigation. Studies of glutamate levels in affective disorders typically focus on the perigenual anterior cingulate cortex, while research on the glutamatergic effects of ketamine has instead focused on a more dorsal portion of the anterior cingulate cortex. It may be that the disorders show divergent glutamatergic abnormalities in the perigenual region, while both being associated with glutamatergic hypofunction in the dorsal region. This would explain the contradictory findings, and explain why ketamine is effective in the treatment of both conditions.

There has been very little work comparing other metabolites between disorders. However one study looking at NAA, a marker of neuronal viability, found no differences between unipolar and bipolar depression (Zhong et al., 2014), suggesting that markers of neuronal integrity may not differentiate the two disorders.

Taken together, these findings suggest that there may be neurochemical differences, but further research is required to properly characterise and evaluate these putative distinct mechanisms, and an important aim for future work will be understanding how different regions of the anterior cingulate cortex may differ in glutamatergic pathology.

## 1.7 Bipolarity as a spectrum

More recently, researchers have begun to consider bipolarity as a spectrum rather than a discrete disorder. On this view, symptoms of hypomania lie on a spectrum between pure unipolar depression with no manic symptoms and full bipolar I disorder with severe manic episodes (Angst, 2007; Cassano et al., 2005). Notably, this indicates that rather than there being a distinction between major depression and bipolar disorder, these conditions may represent positions on a bipolarity spectrum in individuals who suffer from depressive episodes. This view considers bipolar disorder as the co-occurrence of depressive episodes with high levels of bipolarity, as opposed to a condition distinct from depression. Notably, this view has found support in numerous studies showing that many individuals who do not meet traditional criteria for bipolar disorder nonetheless exhibit low level symptoms of hypomania (Angst et al., 2011; Merikangas et al., 2007).

This has important implications for research into the neurobiological basis of mood disorders as it suggests that the aim for research should not necessarily be to identify patterns of abnormalities that distinguish the two disorders, but instead should be to discover alterations in neurobiological systems that correlate with levels of bipolar symptoms within depressed samples. Some promising research using functional neuroimaging has begun to explore this possibility, for example showing that amygdala responses to happy faces correlate with subthreshold hypomanic symptoms in individuals diagnosed with unipolar depression (Fournier et al., 2013), however as yet there is no research into structural or neurochemical alterations that may represent dimensional correlates of bipolarity, and this will be an important question for future research to address.

## 1.8 Limitations of the existing literature and unanswered questions

There are numerous issues with the extant literature that prevent firm conclusions being drawn on the nature of commonalities and differences between major depression and bipolar disorder. This is largely due to the relative immaturity of research into the distinction between these two conditions. First, neuroimaging findings are often inconsistent, and there are still very few direct comparisons between these disorders. This makes it difficult to distinguish between genuine differences in neurobiological systems and noise caused by heterogeneity in patient samples and methods. Research is required to identify the most consistent and robust distinctions between conditions and in the absence of a large body of direct comparisons, meta-analyses have provided one such way to interpret existing research and draw conclusions about how the two diagnoses may compare at the brain level (Kempton et al., 2011; M. J. Taylor, 2014a). More recent advances in meta-analytic methods have allowed the comparison of conditions in a voxelwise manner (Radua, van Den Heuvel, Surguladze, & Mataix-Cols, 2010), and this method could provide a more detailed view of the most robust changes in both unipolar and bipolar disorders.

Second, comparisons are often limited by differences in mood state between conditions, as individuals with major depression tend to be recruited while in a depressed state while those with bipolar disorder are typically scanned while euthymic. Some changes observed in major depression have been shown to be affected by mood state (Arnone et al., 2013) indicating that this can have substantial effects on such abnormalities. This is important because when comparing disorders, it is crucial to determine whether any differences are truly due to disorder-specific processes or are simply an effect of mood state without the confounding effect of treatment. In addition, the most important situation in which an objective diagnostic

biomarker for bipolar disorder would be useful clinically is in the depressed state, as this is when the condition is often mistaken for major depression. Because of this, further comparisons between unipolar and bipolar depression using currently depressed samples are required.

Third, the majority of studies thus far have used patients who are receiving pharmacological treatment. This is a significant limitation because major depression and bipolar disorder are typically treated with different medications, and numerous studies have shown that these medications can affect brain structure and neurochemistry (Arnone et al., 2013; Hajek, Cullis, et al., 2012; Shibuya-Tayoshi et al., 2008; M. J. Taylor et al., 2008), making it possible that differences observed between conditions may simply be an effect of the different types of medication received by patients. It is also possible that non pharmacological treatments can induce brain changes (Kennedy et al., 2007). To address this problem, there is an urgent need for research comparing disorders using medication-free samples. Structural neuroimaging research using unmedicated patients has begun to emerge (Lan et al., 2014), however there are no studies comparing neurochemical alterations in unmedicated bipolar and unipolar depression.

Finally, despite many studies now indicating that characterising bipolarity as a dimensional trait is a more accurate reflection of the psychopathology seen in the real world, there is a lack of research on the neural correlates of dimensional bipolarity, particularly with regard to brain structure and neurochemical makeup. Research into this could provide further evidence for or against the conceptualisation of bipolarity as a spectrum within affective disorders, and could also provide further insights into how structural and neurochemical alterations observed in bipolar disorder relate to the symptoms of the condition.

## 1.9 Relationship to current neurobiological models of affective disorders

These existing findings fit within frameworks explaining affective dysregulation in affective disorders in terms of neurobiological dysfunction in circuits underlying emotion regulation (Mayberg et al., 1997; M. L. Phillips, Ladouceur, & Drevets, 2008; Mary L Phillips & Swartz, 2014; Price & Drevets, 2009; Ressler & Mayberg, 2007). These theories suggest that affective symptoms result from impaired prefrontal-subcortical function, which has been consistently demonstrated in functional neuroimaging work.

This may arise from localised functional impairment due reduced neuronal integrity, as demonstrated by findings of reduced grey matter volume and markers of neuronal viability such as NAA and myo-inositol in areas involved in regulation of affect. Additionally, functional connectivity within these networks appears to be related to their underlying structural connectivity, suggesting that reductions in white matter integrity could lead to functional impairment (de Kwaasteniet et al., 2013). Moreover, alterations in prefrontal glutamatergic and GABAergic neurotransmission may also link to these models of affective disorders through effects on neuronal signalling in prefrontal regions and their connectivity with subcortical structures (Duncan et al., 2013). Taken together, this demonstrates that structural and neurochemical dysfunction can be clearly linked to current models of affective dysregulation in affective disorders

However despite these models being well established and supported by a large body of evidence, there is little theoretical work on the distinction between unipolar and bipolar disorders. Models of both disorders emphasise the importance of prefrontal-subcortical networks in affective dysregulation, which is a key symptom of both conditions. Importantly, however, the way in which these alterations relate to the

emotional lability observed in bipolar disorder is unclear. In particular, while prefrontal-subcortical networks involved in affective regulation have been clearly linked to depressive symptoms, it is not so clear whether they may also play a role in the development of mania. Additionally, despite neurocognitive impairment being an important feature of both disorders (Maalouf et al., 2010), there is little theoretical work on the relationship between structural or neurochemical dysfunction and this cluster of symptoms. Additionally, evidence suggests that cognitive impairment is greater in bipolar than unipolar depression (G. Xu et al., 2012); however, it is unclear how this difference in symptoms might be reflected in neurobiological systems.

In sum, existing models of affective regulation are successful in explaining many of the core symptoms of these disorders. Nonetheless, they do not explain the differences in symptom profiles between unipolar and bipolar disorders, particularly with regard to emotional lability and cognitive impairment in bipolar disorder.

## 1.10 Aims and hypotheses

Together, the research reviewed here indicates that there are clear structural and neurochemical differences between patients with affective disorders and healthy individuals. Studies have begun to move beyond case-control comparisons and are beginning to identify patterns of neurobiological alterations that distinguish major depression and bipolar disorder, an important task given the lack of understanding of their aetiology and the difficulties faced in the diagnosis and treatment of these disorders. However, there is currently a lack of research in this area and existing studies suffer from numerous methodological limitations, making it difficult to draw robust conclusions on common and distinct abnormalities. As a result, theoretical

models are unable to explain differences in symptom profiles between unipolar and bipolar disorders. Finally, it remains to be seen whether the characterisation of bipolarity as a spectrum may yield more informative findings on the neurobiological basis of affective disorders.

Based on this, and the extant literature discussed previously, the present thesis had the following aims and hypotheses:

1) Synthesise the existing large literature on grey and white matter alterations in affective disorders using meta-analysis, to identify the most consistent and robust patterns of change and contrast these between major depression and bipolar. Additionally, use meta-regression to explore the effects of confounding variables such as mood state and pharmacological treatment. I expect to find common reductions in grey matter volume in the prefrontal cortex, while volume reduction in the hippocampus will be specific to unipolar depression. I also expect white matter integrity to be reduced in in the superior longitudinal fasciculus in bipolar depression but intact in unipolar depression.
2) Compare glutamate levels in the prefrontal cortex, as measured using MRS, between unmedicated unipolar and bipolar depression to examine whether glutamatergic alterations are a true marker of bipolarity as opposed to an effect of mood state or medication. I expect to see increased glutamate levels in bipolar depression relative to healthy controls, with reductions in unipolar depression.
3) Explore the relationship between volumetric changes and bipolarity as a spectrum to understand whether treating bipolarity as a dimension may provide further information about the role of grey matter alterations in affective disorders. I expect that grey matter volume regions demonstrating volumetric

differences between conditions in the meta-analysis of grey matter volume will also predict bipolarity as a continuous measure.

# 2 Methods

The methods used for studies undertaken here included meta-analysis, analysis of structural imaging data, and analysis of MRS data. Meta-analyses were used to address the first two aims (synthesis of the existing literature on grey and white matter alterations in unipolar and bipolar depression), with MRS used for the third aim (comparison of glutamate levels between disorders), and structural analysis for the final aim (grey matter correlates of bipolarity as a dimensional trait).

## 2.1 Meta-analyses

### *2.1.1 Literature search*

Extensive literature searches were carried out for both meta-analyses. Inclusion criteria were chosen to be deliberately broad in order to reduce the likelihood of missing relevant studies. Exact search terms, databases, and inclusion criteria differed depending on the aim of the meta-analysis and are provided in the relevant chapters. Additionally, for both meta-analyses reference lists from the included studies as well as relevant review articles and previous meta-analyses were searched for studies not detected by the literature search.

### *2.1.2 Statistical analysis*

Meta-analysis was performed using Anisotropic Effect Size Seed-based *D* Mapping (SDM), a well validated meta-analytic technique for neuroimaging data. This uses either peak coordinates as reported in original studies or statistical maps as inputs and creates voxelwise maps of effect size and variance for each study. Meta-analysis is then performed using traditional random-effects meta-analytic methods in a voxelwise

manner. A major advantage of this method is that it allows heterogeneity to be quantified at each voxel, and this can be further explored with meta-regressions, as in traditional meta-analysis. Statistical significance of results is estimated based on permutation testing.

SDM has several advantages over other commonly used methods such as activation likelihood estimation. Most notable is the ability to perform voxelwise meta-regression, which allows the effects of study characteristics to be evaluated across the brain. Another important advantage of this method is its ability to include studies that find no significant effects, allowing null results to influence analyses and hence limiting positive bias. Other methods, such as activation likelihood estimation, do not include such studies and can therefore give a biased view of the literature. Furthermore, statistical maps can be included in meta-analyses in addition to peak coordinates, and this substantially improves the sensitivity of the analysis.

### *2.1.3 Group comparisons*

SDM was used to perform comparisons between bipolar disorder and major depression in both meta-analyses. This was done in two ways: Firstly, meta-regressions were used to conduct a contrast between the two disorders. This provides an overview of brain regions where in the brain effect sizes differ significantly between conditions, allowing inferences to be made about regions where disorders show divergent patterns of alteration. Secondly, conjunction analyses were used to identify regions in which effect sizes were similar in both conditions. This method identifies voxels where both disorders show a significant change relative to control subjects, while taking into account error in the estimation of the *p* values used to calculate significance. This analysis shows regions where there are either significant increases or decreases in volumes relative to controls in both disorders, suggesting common pathologies.

### *2.1.4 Publication bias*

As SDM produces effect size maps for each study, it is possible to assess publication bias in each significant cluster. To perform this, effect sizes and variances were extracted from the peak voxel of each cluster and funnel plots of this data were produced using the Metafor package in R (www.rproject.org). These were further assessed using Egger's test of funnel plot asymmetry to identify any regions in which the results may be influenced by publication bias.

### *2.1.5 Reliability*

It is important to consider whether the results of a meta-analysis are robust, and are not unnecessarily influenced by individual studies. To ensure that the results of these analyses were reliable, a jack-knife analysis was performed. This involves iteratively repeating the analysis removing one study at a time, and assessing the effects of this on the overall results. Reliable results should be robust to this process and therefore remain present across the majority of iterations, while less robust effects will disappear frequently. Clusters were only accepted if they remained present in 90% of jack-knife iterations.

In addition to this analysis, funnel plots were visually inspected to ensure that clusters were not being driven by outlying results, and significant clusters were only accepted if 25% of studies found an effect in the region. This protects against the possibility of clusters being caused by large effect sizes in a minority of studies, and instead ensures that all clusters are representative of the literature as a whole.

### *2.1.6 Meta-regressions*

Meta-regressions were performed with clinical and demographic variables of interest, when they were reported in a sufficient proportion of the original studies. Exact

variables included are detailed in further chapters, but these typically included measures of illness duration and severity, along with age and sex. These were explored only in regions where significant heterogeneity in effect sizes was observed, and where there was a main effect of the disorder of interest.

### *2.1.7 Significance thresholding*

The threshold for main analyses was set at $p < .005$ uncorrected with a peak Z value of 1 and an extent of 10 voxels, as previous research has shown that this confers an optimal balance of sensitivity and specificity. As meta-regression analyses are often susceptible to false positives, a more conservative threshold of $p < .0005$ was used in these analyses. For group comparisons, as the sample in each group was large, reducing the likelihood of false positives being produced, a threshold of $p < .001$ was used. For conjunction analyses, the threshold was set at $p < .005$, without the correction proposed by Radua et al, in order to test the conjunction null (i.e. inferring that the effect is present in both conditions) as opposed to the global null (i.e. inferring that there is an effect in at least one condition).

## 2.2 Neuroimaging

### *2.2.1 Ethics*

Ethical approval for the imaging study was obtained from the Bromley NHS Research Ethics Committee. All subjects provided written informed consent and were financially compensated for participation.

### *2.2.2 MRS Sample*

Inclusion criteria for patients were as follows: diagnosis of major depression or bipolar disorder, currently in a depressed state, no current pharmacological or psychological treatment, no other primary mental health problems, no significant physical health problems, any use of illicit substances in the previous two months, any current use of medication that may affect neuropsychological function, no neurological problems, no MRI contraindications. Patients were recruited both through local psychological therapies services and online advertisements to the general public (Wise, Arnone, Marwood, et al., 2016a).

Healthy control participants were recruited through online advertisements and word of mouth. Inclusion criteria for healthy controls were as follows: no personal history of mental health problems, no history of mental health problems in first degree relatives (as judged by patients' reports), no significant physical health problems, any use of illicit substances in the previous two months, any current use of medication that may affect neuropsychological function, no neurological problems, no MRI contraindications.

All participants were screened for exclusion criteria by a phone interview, and potential participants were invited for a full screening interview. Diagnosis was made according to DSM-IV criteria based on detailed clinical interview using the Mini International Neuropsychiatric Interview (MINI, Sheehan et al., 1998), supplemented by review of case notes and collateral information where necessary. As part of this interview, a full history was taken to evaluate past symptoms of mania, and exclude any other potential explanation for symptoms, such as drug use. This process was important as it was crucial to ensure that diagnosis of unipolar versus bipolar depression was as accurate as possible. Comorbidities were assessed using the Mini

International Neuropsychiatric Interview (MINI). Demographic and clinical details for this sample are provided in the relevant chapters.

### *2.2.3 Structural sample*

For the analysis of the structural neuroimaging data, a second sample of individuals with unipolar depression was recruited to supplement the sample used for the MRS analyses. The inclusion and exclusion criteria for both patients and healthy controls in this sample were largely identical to the first sample, however comorbid anxiety disorders were not an exclusion criterion. Patients in this sample were also recruited using the same methods as the first sample. Demographic and clinical details for this sample are provided in the relevant chapter.

### *2.2.4 Questionnaire measures*

Depression severity was assessed using both the 21 item Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS)(Montgomery & Asberg, 1979), while levels of current manic symptoms in patients diagnosed with bipolar disorder were recorded using the Young Mania Rating Scale (Young, Biggs, Ziegler, & Meyer, 1978). Levels of trait hypomanic symptoms were measured using the Hypomania Checklist (HCL)(Angst et al., 2005, p. 32; Feng et al., 2016). This scale was developed as a screening tool for bipolar disorder, and has excellent sensitivity for the condition (Angst et al., 2005). However subsequent research has also found that this tool is effective as a measure of hypomanic symptoms regardless of bipolar diagnosis, and recent studies have used this as a measure of bipolarity with success (Yang et al., 2016).

### *2.2.5 MRS*

Glutamate concentrations were quantified with $^{1}$H-MRS using a voxel placed in the dorsal anterior cingulate cortex. MRS allows the concentration of a range of neurometabolites to be measured in vivo, and the method is able to quantify glutamate levels with accuracy. These concentrations are determined based on the resonant frequencies of hydrogen atoms within a magnetic field. The resonant frequency of a particular atom is dependent on the substance it is contained within, and MRS produces a spectrum of metabolites based on this variation in frequencies. A model can be fitted to this data using software such as LCModel (Provencher, 2001) which then provides concentrations of each metabolite. An example spectrum, with fitted model and concentrations of metabolites, is shown in Figure 2-1.

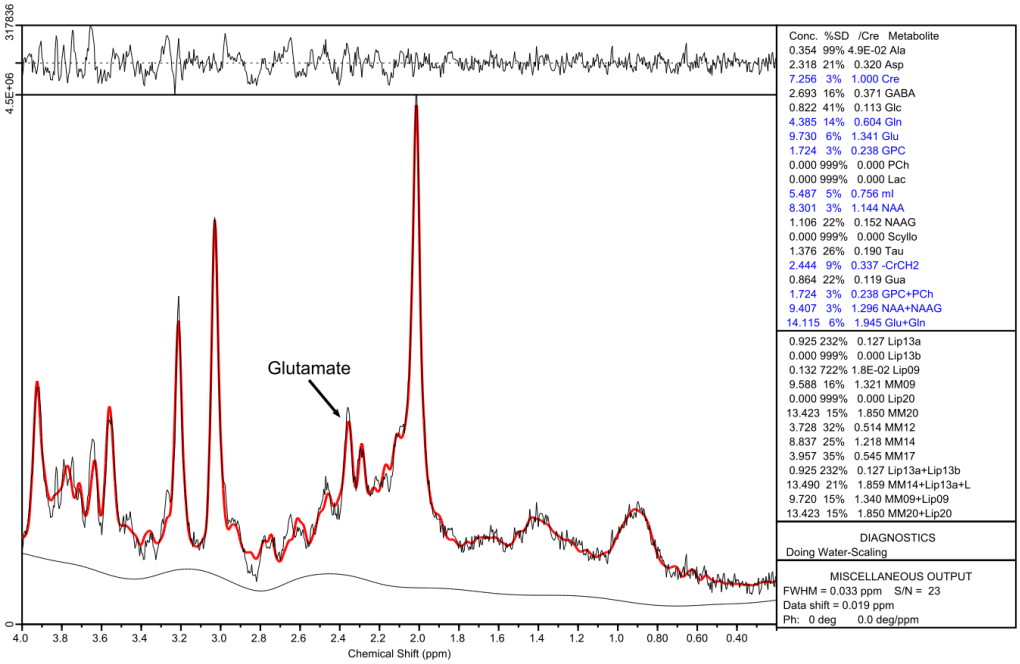


**Figure 2-1. Example MRS spectrum with fitted model and metabolite concentrations**

Data for the study presented here were acquired on a 3-Tesla scanner (further details regarding the sequence used are presented in the Chapter 5). The ability of MRS to separate metabolites with similar resonant frequencies relies on the field strength used, and 3-Tesla has been demonstrated to be sufficient to distinguish glutamate from

glutamine (Schubert, Gallinat, Seifert, & Rinneberg, 2004b). This provided a measure of glutamate levels, uncontaminated by glutamine, the other component of the glutamate-glutamine cycle.

One issue in measuring glutamate levels using MRS is variation in detected glutamate levels due to structural content of the voxel chosen. For example, as glutamate is predominantly present in grey matter, a voxel with a greater proportion of grey matter will show higher levels of glutamate. This is particularly problematic if comparing healthy individuals to a patient group who demonstrate alterations in grey matter volume. To avoid this problem, ratios of glutamate to creatine were used here. Creatine is also present in grey matter but is not linked to the pathology of affective disorders (Arnone, Mumuni, Jauhar, Condon, & Cavanagh, 2015), making it a suitable metabolite to normalise glutamate levels to.

### *2.2.6 Voxel-based morphometry*

In order to examine the relationship between grey matter volume and bipolarity, grey matter volume was quantified using voxel-based morphometry (VBM) (Ashburner, 2007; Ashburner & Friston, 2000). VBM allows grey matter volume to be assessed in a voxelwise manner, meaning that local patterns of volumetric changes can be identified. This is in contrast to other methods of detecting volumetric change, which rely on the manual or automatic measurement of entire brain regions, potentially disguising small areas of volumetric alteration.

Voxel-based morphometry involves first segmenting an individual's structural image into grey matter, white matter and cerebrospinal fluid and normalising these images to a template to allow comparison across subjects. To provide a measure of the volume in a given voxel, the proportion of grey matter in this voxel is scaled by the degree to

which the region is warped to match the template in a step referred to as modulation. The resulting voxelwise grey matter volume maps can then be used in further analyses. In the analysis presented here, these whole-brain maps of grey matter volume were entered as features into machine learning analyses.

### *2.2.7 Machine learning*

Recent studies in psychiatry have indicated that machine learning methods offer a novel way to address important challenges in the area (Huys, Maia, & Frank, 2016). For example, the majority of psychiatric research has focused on determining alterations in a particular disorder based on comparing group averages (such as average grey matter volume in a particular brain region), but this has not provided any clinical advances as it does not allow predictions to be made at the level of the individual patient. In contrast, machine learning approaches have allowed the diagnostic classification of individual patients and prediction of an individual's symptoms based on brain imaging.

An additional advantage of these approaches is their multivariate nature, which allows the detection of distributed patterns of alteration that may be missed be traditional univariate approaches that consider each voxel in the brain independently. This could result in more accurate representations of the true nature of relationships between volumetric changes and psychiatric symptoms.

Here, support vector regression (Smola & Vapnik, 1997) was used to predict hypomanic symptoms from grey matter volume at the individual patient level. This method is described in more detail in Chapter 6, but in brief, it allows the prediction of a continuous variable such as hypomanic symptoms from a large number of input variables, or features, such as grey matter in a selection of voxels in the brain. As a

result, this method is perfectly placed to answer the question of whether grey matter volume is associated with bipolar symptoms.

# 3 Voxel-Based Meta-Analytical Evidence of Structural Disconnectivity in Major Depression and Bipolar Disorder

*As published in Biological Psychiatry (Wise, Radua, Nortje, et al., 2016). Supplemental material accompanying the paper is presented at the end of the chapter.*

## 3.1 Introduction

Affective disorders such as major depression and bipolar disorder are common and disabling conditions (Kessler et al., 2003; Merikangas et al., 2007) with uncertain biological aetiological mechanisms. Understanding the pathophysiology of these disorders is likely to be key to the development of more effective treatments, thus investing in this type of work has become a research priority. In recent years much progress has originated from neuroimaging research in affective disorders indicating that certain brain circuits are likely to be involved in the regulation of affective states (M. L. Phillips et al., 2008; Wise et al., 2014). Multimodal neuroimaging evidence has shown an integrated pattern of brain abnormalities in affective disorders in regions such as the prefrontal cortex, the limbic system (e.g. the amygdala), the ventral striatum, the insula and the hippocampus (Arnone, McIntosh, et al., 2012; Bora et al., 2012; Delvecchio et al., 2012; Selvaraj et al., 2012). A recent major step forward in the field has been the realization that aberrant structural and functional connectivity between these regions is likely to be as crucial to the pathogenesis of these conditions as isolated changes in volume and functional activity (Greicius et al., 2007; Korgaonkar, Fornito, Williams, & Grieve, 2014; Townsend et al., 2013). There is however particular uncertainty about the consistency and replicability of findings in relation to white matter abnormalities in affective disorders (Liao et al., 2013; Nortje, Stein, Radua, Mataix-Cols, & Horn, 2013). This is due to the more recent introduction

of diffusion tensor imaging (DTI) techniques such as tract-based spatial statistics (TBSS), the paucity of studies in affective disorders and the substantial variability in clinical samples. Also very little is known about whether unipolar and bipolar disorders are associated with common or distinct changes in structural connectivity, largely due to the rarity of direct comparisons between unipolar and bipolar disorders (Versace et al., 2010b).

Therefore, the focus of this work was to reliably identify white matter abnormalities in affective disorders by taking advantage of the larger number of studies published in recent years. This was accomplished by including all available DTI methods, voxel-based analysis (VBA) and TBSS techniques and by using a novel meta-analytic technique that allows effect size estimations to compare effect sizes between unipolar and bipolar disorders (Radua et al., 2014).

A thorough conservative approach was implemented in this work, complemented by sensitivity and meta-regression analyses, conducive to reliable identification of the most robust findings within a highly heterogeneous literature.

## 3.2 Methods

### *3.2.1 Literature Searches*

Literature searches were conducted by using 'Pubmed', 'Embase' and 'Scopus' to identify diffusion tensor imaging literature in affective disorders published up to January 2014 with the following search terms: 'Depression' or 'Bipolar' or 'Mania', and 'Diffusion tensor imaging' or 'DTI'. Studies were systematically inspected to identify measures of water diffusion and were cross-referenced for inclusiveness. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009) in this meta-analysis. Exclusion criteria were: 1) age below 18 or above 65, to minimize the effect of neurodevelopment and neurodegeneration as potential confounders on white matter diffusivity (Barnea-Goraly et al., 2005; Glahn et al., 2013); 2) studies looking at affective disorders in the context of neurological disorders, to ensure that findings were not due to neurological pathology; 3) articles that used a region of interest approach, did not use consistent statistical thresholds throughout the brain or did not report peak coordinates. The following selection algorithm was followed to avoid sample overlaps: 1) the largest sample was included in case of multiple studies using the same patient group; 2) only the results from the entire group of participants were considered in case of multiple sub-analyses from the same group of patients; 3) only pre-treatment data were included in case of longitudinal studies.

### *3.2.2 Meta-analysis*

Anisotropic Effect Size-Signed Differential Mapping (AES-SDM) (Radua et al., 2014) was adopted for this meta-analysis. As previously described (Radua et al., 2012; Radua & Mataix-Cols, 2009) AES-SDM creates effect size and variance maps based on peak coordinates reported in studies, which are then analyzed with traditional random-effects meta-analytic methods. In addition, this technique allows heterogeneity maps to be generated, and meta-regressions to be conducted across the whole brain. Importantly, AES-SDM also allows meta-analytic group comparisons, which provides an indication of where computed effect sizes differ significantly between groups (Radua et al., 2010). Taking advantage of this approach, effect size comparisons were conducted between unipolar and bipolar disorders and VBA and TBSS DTI methods (see Supplementary Methods). Brain regions where unipolar and bipolar disorders differed from healthy controls were further confirmed with a

conjunction analysis using AES-SDM's multi-modal analysis function. This method identifies regions in which two separate meta-analyses both produce significant results, accounting for error in the estimation of the meta-analyses' *p* values (Radua, Romeo, Mataix-Cols, & Fusar-Poli, 2013).

When comparing diagnostic groups, potential differences in clinical and demographic variables between groups were assessed with regular meta-regressions weighted by sample size. The proportion of studies using TBSS and VBA methods was compared using $X^2$ tests. We performed similar analyses to highlight potential confounding variables when comparing DTI methods, based on variables which were shown to moderate FA differences in meta-regressions.

We took a thorough and detailed approach to ensure that only the most replicable and robust of the results were retained. Firstly, a jack-knife sensitivity analysis was conducted. This involves repeating the analyses with one study removed per iteration to assess the contribution of each study to the results. Results that no longer reached significance in two or more iterations were rejected. In addition, to confirm that findings were reliable, funnel plots were visually inspected. Together, these steps limited the influence of outlying results. To examine publication bias, asymmetry of funnel plots was tested using Egger's test (Egger, Smith, Schneider, & Minder, 1997) as implemented in the Metafor package (Viechtbauer, 2010) for R software (http://www.r-project.org/).

A threshold of $p = .005$ with peak $Z > 1$ and a cluster extent of $> 10$ voxels was used for the meta-analyses and heterogeneity analyses and a more conservative threshold of $p = .0005$ was adopted for meta-regression and group comparison analyses to provide the optimal balance of sensitivity and specificity as suggested by Radua and others (Radua et al., 2012).

To aid the identification and visualization of the tracts affected, the results of the analyses were projected on to a high resolution diffusion MRI dataset generated from 80 subjects of the Human Connectome Project (Van Essen et al., 2012) using DSI Studio (http://www.dsi-studio.labsolver.org). We used a 3D atlas of human white matter tracts (Catani & de Schotten, 2012) to identify the implicated tracts. All coordinates are presented in Montreal Neurological Institute (MNI) space.

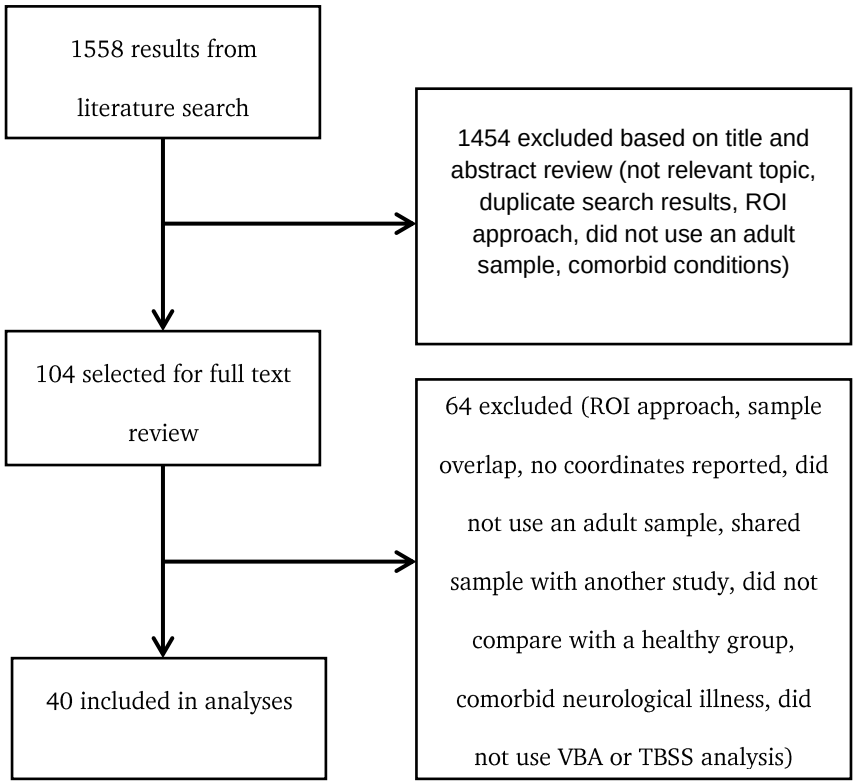


**Figure 3-1. Literature search methods and results. Abbreviations: TBSS, tract-based spatial statistics, VBA, voxel-based analysis, ROI, region of interest.**

| Study | Analysis Method | Major Depression Patients | | | | | | | Healthy Controls | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *N* | Age (mean) | Sex (M,F) | Illness duration (y) | HAMD-17 | Antidepressants (%) | State | *N* | Mean Age | Sex (M, F) |
| Abe et al., 2010 | VBA | 21 | 48.1 | 11, 10 | 6 | 9.2 | 48 | 7 Depressed, 14 remitted | 42 | 48 | 22, 20 |
| Arnold et al., 2012 | VBA | 17 | 30.4 | 4, 13 | - | 9.2 | 0 | Remitted | 21 | 26.9 | 7, 14 |
| Bracht et al., 2012 | VBA | 22 | 44.8 | 11, 11 | - | 21.6 | 91 | Depressed | 21 | 41.4 | 9, 12 |
| Choi et al., 2014 | TBSS | 134 | 38.5 | 64, 70 | 9.3 | 11.7 | 0 | Depressed | 54 | 34.4 | 28, 26 |
| Dalby et al., 2010 | VBA | 22 | 57.4 | 7, 15 | - | - | - | Depressed | 22 | 59.2 | 7, 15 |
| Wen-bin Guo, Liu, Chen, et al., 2012 | TBSS | 22 | 28.1 | 12, 10 | 0.3 | 25.9 | 0 | Depressed | 19 | 24.4 | 10, 9 |
| Wen-bin Guo, Liu, Xue, et al., 2012 | TBSS | 23 | 27.4 | 11, 12 | 2.3 | 24.5 | 100 | Depressed | 19 | 24.4 | 10, 9 |
| Jia et al., 2010 | VBA | 52 | 34.6 | 25, 27 | - | 23 | 0 | Depressed | 52 | 37.1 | 24, 28 |
| Kieseppä et al., 2003 | TBSS | 16 | 48.4 | 2, 14 | 14.1 | - | 81 | Depressed | 20 | 42 | 10, 10 |
| Korgaonkar et al., 2011 | TBSS | 29 | 40.5 | 12, 17 | - | 19.1 | 0 | Depressed | 39 | 29.6 | 18, 21 |
| M. D. Ma Ning et al., 2007 | VBA | 14 | 28.9 | 2, 12 | 0.9 | - | 0 | Depressed | 14 | 27.1 | 2, 12 |
| Murphy et al., 2012 | TBSS | 45 | 42.6 | 16, 29 | 14.6 | - | 67 | Depressed | 45 | 36.5 | 17, 28 |
| Osoba et al., 2013 | VBA | 20 | 38.3 | 12, 8 | - | 12.2 | 100 | Depressed | 20 | 33.8 | 17, 3 |
| Ouyang et al., 2011 | VBA | 18 | 27.4 | 9, 9 | 1.3 | 24.2 | 0 | Depressed | 18 | 27 | 9, 9 |
| Hong-jun Peng et al., 2013 | VBA | 30 | 26.8 | 19, 11 | 4.7 | - | 0 | Depressed | 25 | 28.2 | 14, 11 |
| Seok et al., 2013 | TBSS | 86 | 44.7 | 18, 68 | 3.6 | 14.6 | 52 | Depressed | 62 | 42 | 21, 41 |
| Tha et al., 2013 | VBA | 19 | 38.6 | 12, 7 | 1.5 | 19 | 0 | Depressed | 19 | 36.5 | 13, 6 |
| Versace et al., 2010b | TBSS | 16 | 32.9 | 4, 12 | 14.7 | 17.1 | 88 | Depressed | 24 | 27.7 | 9, 15 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| T. Wang et al., 2013 | VBA | 21 | 29.6 | 5, 16 | 1.2 | 20.4 | 0 | Depressed | 22 | 30.2 | 8, 14 |
| Wu et al., 2011 | VBA | 23 | 31.4 | 10, 13 | 0.2 | 21.8 | 0 | Depressed | 21 | 30.4 | 9, 12 |
| Zhu et al., 2011 | TBSS | 25 | 20.6 | 11, 14 | 1.1 | - | 0 | Depressed | 25 | 20.3 | 11, 14 |
| Zou et al., 2008 | VBA | 45 | 33.2 | 15, 30 | 1.7 | 23.8 | 100 | Depressed | 45 | 31 | 15, 30 |
| Zuo et al., 2012 | TBSS | 16 | 37 | 3, 13 | - | 21.5 | 0 | Depressed | 19 | 36.6 | 7, 12 |

**Table 3-1 Characteristics of MDD studies included in the meta-analysis. Abbreviations: TBSS, tract-based spatial statistics, VBA, voxel-based analysis, HAM-D 17, Hamilton depression rating scale 17-item.**

| | | Bipolar Disorder Patients | | | | | | | | | Healthy Controls | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Analysis Method** | ***N*** | **Age (mean)** | **Sex (M,F)** | **Illness duration (y)** | **HAMD-17** | **YMRS** | **Lithium (%)** | **Subtype** | **State** | ***N*** | **Mean Age** | **Sex (M,F)** |
| Benedetti, Yeh, et al., 2011 | TBSS | 40 | 46.1 | 10, 30 | 15 | 16 | - | 35 | BD-I | Depressed | 21 | 39.9 | 22, 20 |
| S. Bruno, Cercignani, & Ron, 2008 | VBA | 36 | 39 | 13, 23 | - | - | - | 63 | 25 BD-I, 11 BD-II | - | 28 | - | 7, 14 |
| Canales-Rodríguez et al., 2014 | VBA | 40 | 40.6 | 25, 15 | 15.9 | - | 1.4 | 75 | BD-I | Euthymic | 40 | 40.4 | 9, 12 |
| Chaddock et al., 2009 | VBA | 19 | 43.3 | 9, 10 | 15.6 | - | - | 47 | BD-I | Euthymic | 18 | 41.7 | 28, 26 |
| Chan et al., 2010 | TBSS | 16 | 36.9 | 12, 4 | 0.2 | - | 3.8 | 37 | BD-I | Euthymic | 16 | 37.3 | 7, 15 |
| Z. Chen et al., 2012 | VBA | 18 | 32 | 18, 0 | 4.2 | 3.2 | 24.8 | 83 | BD-I | Manic | 27 | 31.3 | 10, 9 |
| Cui, Chen, et al., 2011 | VBA | 18 | 27.9 | 10, 8 | 4.8 | - | 25.9 | - | BD-I | Manic | 30 | 23.9 | 10, 9 |
| Ha et al., 2011 | VBA | 12 | 37.3 | 3, 9 | 13.3 | - | 1.4 | 66 | BD-I | Euthymic | 22 | 34.7 | 24, 28 |
| Lagopoulos et al., 2013 | TBSS | 58 | 23 | 17, 41 | 7.5 | 13.4 | - | - | 18 BD-I, 27 BD-II, 13 BD-NOS | Depressed | 40 | 24.1 | 10, 10 |
| Liu et al., 2010 | VBA | 27 | 35.4 | 9, 18 | 8. 3 | 6.7 | 0.9 | 14 | 14 BD-I, 13 BD-II | Euthymic | 21 | 38.3 | 18, 21 |
| Lu, Zhou, Keedy, Reilly, & Sweeney, 2011 | VBA | 13 | 25 | 7, 6 | - | - | 24 | 0 | BD-I | Manic | 18 | 24 | 2, 12 |
| Mahon et al., 2009 | VBA | 30 | 33.4 | 15, 15 | - | - | - | - | 25 BD-I, 2 BD-II, 3 BD-NOS | - | 38 | 31.9 | 17, 28 |
| Mahon, Burdick, Wu, Ardekani, & Szeszko, 2012 | TBSS | 29 | 35 | 18, 11 | 12.1 | - | - | - | BD-I | Euthymic | 15 | 33.7 | 17, 3 |
| Sprooten et al., 2013 | TBSS | 64 | 31.7 | 18, 46 | 10 | - | 1 | 19 | BD-I | Euthymic | 46 | 30.1 | 9, 9 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sussmann et al., 2009 | VBA | 42 | 39.6 | 22, 20 | - | - | 0.6 | 57 | BD-I | Euthymic | 38 | 37.2 | 14, 11 |
| Versace et al., 2010b | TBSS | 15 | 36.3 | 1, 14 | 14.7 | 14.9 | - | - | BD-I | Depressed | 24 | 27.7 | 21, 41 |
| Wessa et al., 2009 | TBSS | 22 | 45.4 | 11, 11 | 22 | 0.1 | 0.9 | 45 | 14 BD-I, 8 BD-II | Euthymic | 21 | 43 | 13, 6 |
| Zanetti et al., 2009 | VBA | 37 | 34.1 | 13, 24 | 11.6 | 6.4 | - | 32 | BD-I | 16 depressed, 21 euthymic | 26 | 28.8 | 9, 15 |

**Table 3-2. Characteristics of bipolar disorder studies included in the meta-analysis. Abbreviations: TBSS, tract-based spatial statistics, VBA, voxel-based analysis, HAM-D 17, Hamilton depression rating scale 17-item, YMRS, Young mania rating scale.**

## 3.3 Results

### *3.3.1 Literature searches*

Search criteria were intentionally broad to ensure that the searches were comprehensive and inclusive. This resulted in 1558 studies being identified, with 40 meeting criteria for inclusion in the analysis (see Figure 3-1 for details). Only one study compared both major depression and bipolar disorder with controls (Versace et al., 2010b). Among the range of measures derived from DTI, fractional anisotropy (FA) was the only one consistently reported in all the studies and was therefore the only one examined in this meta-analysis.

### *3.3.2 Sample characteristics*

#### 3.3.2.1 MAJOR DEPRESSION

Twenty-three studies were included in the analysis (Table 3-1), resulting in 736 patients and 668 controls. At the time of scanning 705 (96%) patients were currently depressed, and 31 remitted (4%). The mean age for patients was 33.7 years, 295 (40%) were male, 220 (29%) were medicated, and the mean HAM-D 17 score was 18.8. Demographic details were well reported, while reporting of clinical variables was inconsistent.

#### 3.3.2.2 BIPOLAR DISORDER

Eighteen studies were included in the analyses (Table 3-2), which combined 536 patients and 489 controls. Of the patients, 129 (24%) were depressed at the time of scanning, 292 (55%) were euthymic, 49 (9%) were manic, and mood state was not specified for 66 (12%). In relation to bipolar subtypes 459 patients were type I, 61 were type II and in 16 the subtype was non-otherwise-specified. The mean age of patients was 33.4 years, 231 (43%) were male, mean HAM-D 17 score was 6.3 and

mean YMRS score was 8.5. Demographic variables were well reported but the quality of reporting of clinical variables varied. Four hundred and eighty patients (90%) were reported to be medicated, 166 of them with lithium (31%).

#### 3.3.2.3 MAJOR DEPRESSION VS. BIPOLAR DISORDER

Bipolar disorder and unipolar depression patients were similar in respect of sex ($Q_M^{(1)} = 1.21$, $p = .27$) and mean age ($Q_M^{(1)} = 1.21 = 0.03$, $p = .85$). Duration of illness was greater in bipolar disorder ($Q_M^{(1)} = 11.71$, $p < .001$). The proportion of studies that used VBA and TBSS methods did not differ between the two conditions ($X^2_{(1)} = 0.30$, $p = .58$). Predictably the proportion of depressed patients was higher in the depressed group as the majority of bipolar patients were euthymic at the time of scanning ($Q_M^{(1)} = 52.61$, $p < .001$).

### *3.3.3 Changes in fractional anisotropy*

#### 3.3.3.1 MAJOR DEPRESSION VS. HEALTHY CONTROLS

Only results from group comparisons that met our criteria for robustness are reported in the text, and full details for all clusters are available in Table 3-3. Patients with major depression showed a cluster of decreased FA vs. controls with the peak voxel in the left genu of the corpus callosum (MNI coordinates: -6, 26, 10; *Z*: -2.10; p<0.001; 253 voxels) that survived all iterations of the jack-knife analysis and met our criteria for robustness (Figure 3-2 and Table 3-3). This area did not show significant between study heterogeneity (all P values > .005). Inspection of funnel plots did not show any presence of publication bias, and Egger's tests were non-significant ($p > .05$). There were no clusters of increased FA that survived jack-knife analysis (Table 3-3).

#### 3.3.3.2 BIPOLAR DISORDER VS. HEALTHY CONTROLS

Patients with bipolar disorder showed clusters of decreased FA vs. healthy individuals with peak voxels centered in the left cingulum (MNI: -12, -36, 38; *Z*: -2.72; p<0.001;

325 voxels), in the right anterior superior longitudinal fasciculus (MNI: 30, 26, 16; *Z*: -1.62; p<0.001; 26 voxels) and the left genu of the corpus callosum (MNI: -8, 32, 4; *Z*: -2.06; p<0.001; 241 voxels) meeting criteria for robustness. The corpus callosum cluster extended laterally incorporating fibers joining left uncinate fasciculus, anterior thalamic radiation, cingulum and inferior fronto-occipital fasciculus (Figure 3-2). The cingulum cluster also included parts of the corpus callosum that connect the left and right somatosensory and motor cortices, although the cluster did appear to extend along the length of the cingulum rather than the corpus callosum suggesting that it is the cingulum that is most affected. There were no clusters of increased FA that survived jack-knife analysis (Table 3-3).

In the areas described above significant between-study heterogeneity was identified in the left cingulum ($Z = 3.85$, $p < .001$) and in the left genu of the corpus callosum ($Z = 2.17$, $p < .001$). Meta-regression analysis suggested that the reduction in FA measured in the left cingulum was less pronounced with increasing age (slope peak = -18, -34, 36, $Z = 4.59$, $p < .001$). There were too few studies to perform group comparisons of bipolar subtypes or mood states. Subgroup sensitivity analyses of bipolar subtype and mood state confirmed the robustness of the three clusters identified in the original analysis which remained significant when limiting the analysis to only bipolar type 1 or only euthymic samples.

#### 3.3.3.3 MAJOR DEPRESSION VS. BIPOLAR DISORDER

Comparison of effect sizes revealed significant differences in the left cingulum, where bipolar patients showed greater reductions in FA in comparison with unipolar depressed participants (peak voxel MNI = 16, -34, 34, $Z = 2.77$, $p < .001$). Conjunction analysis confirmed that the genu of the corpus callosum, extending into the left prefrontal white matter (peak voxel, MNI = -6, 28, 10, $d = -1.46$, $p < .001$),

was the only area where both conditions demonstrated significantly reduced FA. These clusters and the tracts implicated are shown in Figure 3-3.

#### 3.3.3.4 TBSS VS. VBA METHODS

As compared to studies using VBA, studies using TBSS detected more pronounced reductions of FA in the genu of the corpus callosum in major depression (peak MNI = -2, 28, 10, $Z = 1.45$, $p < .001$) and in the left cingulum in bipolar disorder (peak MNI = -18,-28, 32, $Z = 3.05$, $p < .001$). Mean patient age, shown to moderate effect sizes in the cingulum in bipolar patients, did not differ between TBSS and VBA studies ($Q_M^{(1)} = 0.11$, $p = .74$) suggesting an unlikely contribution to the measured differences in DTI techniques.

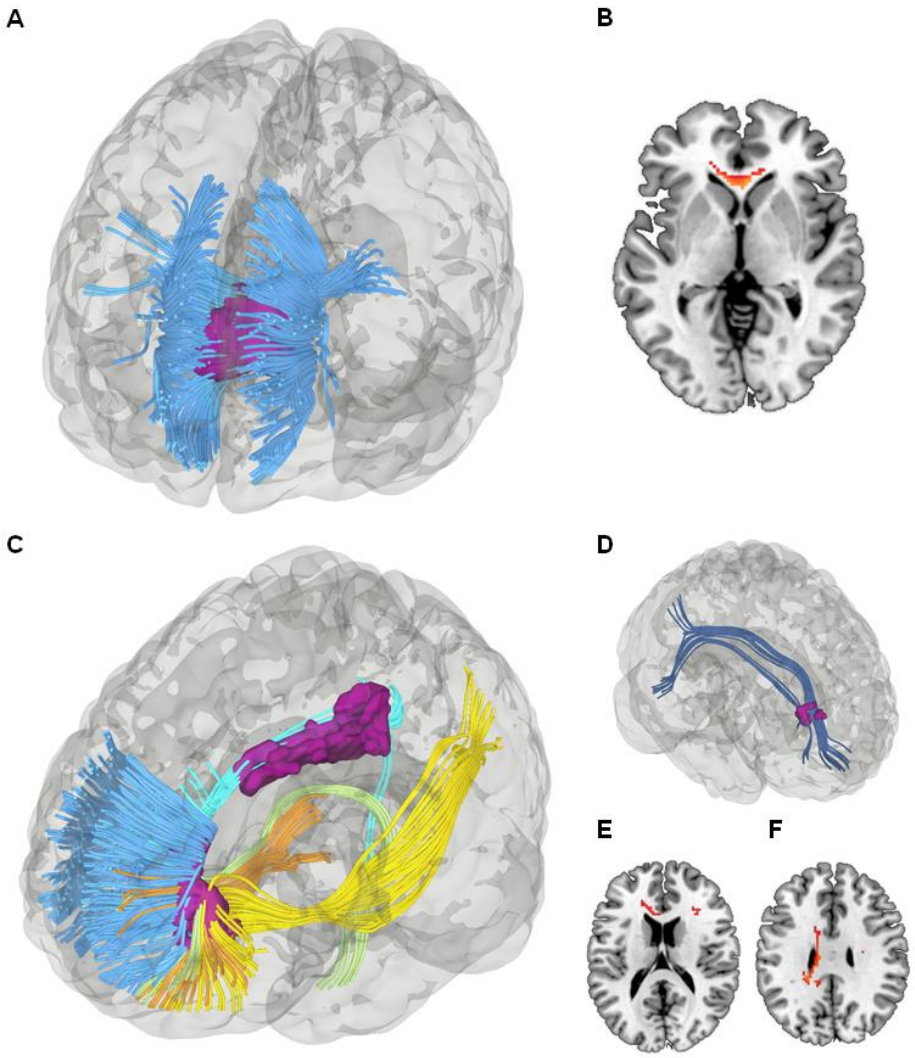


**Figure 3-2.** A: 3D Illustration of the tracts present in the cluster centered on the genu of the corpus callosum in major depression. Medium blue = anterior callosal fibers including the forceps minor. Clusters showing significant effects are in purple. B: 2D representation of the significant clusters in the bipolar disorder (BD) analysis. C: 3D Illustration of the tracts present in the genu of the corpus callosum cluster and cingulum cluster in BD. Light blue = cingulum, medium blue = anterior callosal fibers including the forceps minor, orange = anterior thalamic radiation, green = uncinate fasciculus, yellow = inferior fronto-occipital fasciculus. For illustrative purposes, the area of the dorsal corpus callosum affected by the cingulum cluster is not displayed. D: 3D Illustration of the cluster encompssing the superior longitudinal fasciculus in BD. E: 2D representation of the corpus callosum and superior longitudinal fasciculus clusters in the BD analysis. Red areas represent decreased fractional anisotropy compared with controls. F: 2D representation of the cingulum cluster in the BD analysis.

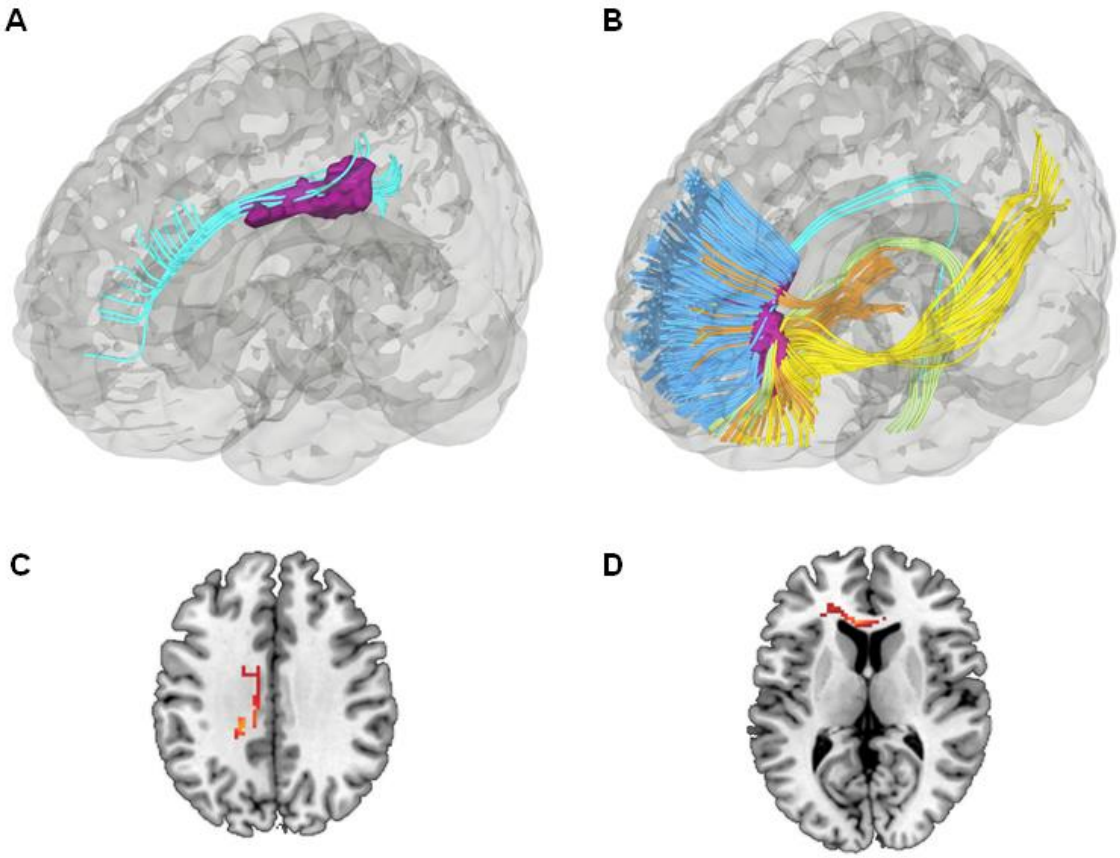


Figure 3-3. A: 3D Illustration of the tracts present in the cluster cantered on the left posterior cingulum in the major depression (MDD) vs. bipolar disorder (BD) analysis. Light blue = cingulum. Clusters showing significant effects are in purple. B: 3D illustration of the tracts present in the cluster centered on the genu of the corpus callosum in the MDD & BD conjunction analysis. Light blue = cingulum, medium blue = anterior callosal fibers including the forceps minor, orange = anterior thalamic radiation, green = uncinate fasciculus, yellow = inferior fronto-occipital fasciculus. C: 2D representation of the result of the MDD vs. BD comparison. Red areas represent decreased fractional anisotropy in BD relative to MDD. D: 2D representation of the result of the MDD & BD conjunction analysis. Red areas indicate areas which showed decreased fractional anisotropy in both conditions.

## 3.4 Discussion

In this voxel-based meta-analysis of DTI studies, the largest to date in affective disorders, incorporating VBA and TBSS studies, we demonstrated that both major depression and bipolar disorder are associated with reduced FA in the genu of the corpus callosum, suggesting that decreased white matter microstructural integrity in this region is common to both disorders. Furthermore effect size comparison between bipolar and unipolar disorders indicated a distinctive white matter microstructural difference in the left posterior cingulum where bipolar patients showed a reduction in FA. The comparison between TBSS and VBA studies indicated that the former technique might be more sensitive in detecting greater FA reductions in the areas where differences were measured in both conditions.

This work expands on findings from previous DTI meta-analyses in affective disorders (Liao et al., 2013; Nortje et al., 2013) in a number of ways. Firstly, we were able to include a much larger number of published studies than previously reported, including TBSS studies. This is likely to result in decreased chance of type I/II errors and increased precision of effect size estimates; secondly, the inclusion of negative findings is inbuilt in the methodology used, in contrast to Activation Likelihood Estimation techniques used in some previous analyses (Liao et al., 2013), further reducing the risk of false positives; thirdly, we went to greater lengths than previous meta-analyses to ensure that our findings were robust and reliable by excluding any findings that jack-knife sensitivity analyses and visual inspection of the results suggested were not sufficiently reproducible. Coordinate-based meta-analyses can in fact produce spurious findings due to difficulties in estimating statistical significance. Thus we set out to identify the most consistent and reliable white matter differences in affective

disorders, rather than pursuing a more exploratory approach used by previous meta-analyses (Liao et al., 2013; Nortje et al., 2013).

The measured reduction in FA in the genu of the corpus callosum in both unipolar and bipolar disorders suggests that impaired prefrontal inter-hemispheric structural connectivity may represent a common pathophysiological pathway in affective disorders. The genu of the corpus callosum is a functionally relevant area through which anterior commissural fibers, including the forceps minor, pass connecting the two hemispheres of the prefrontal cortex. Relevant prefrontal areas include the medial prefrontal cortices and the anterior cingulate cortex, which are central to current theories of mood dysregulation in affective disorders (M. L. Phillips et al., 2008; Wise et al., 2014) and where morphometric (Arnone et al., 2009; Bora et al., 2012) and functional abnormalities (Diener et al., 2012; Houenou et al., 2011) have been consistently reported. Decreased structural connectivity between these regions may constitute a common pathway to mood dysregulation in both conditions.

Interestingly, in the analysis in bipolar patients, the cluster centered in the genu of the corpus callosum also included a number of other tracts including the uncinate fasciculus. This tract connects the prefrontal cortex to medial temporal lobe regions including the amygdala and hippocampus, and decreased integrity in this tract may thus provide a structural basis for the altered fronto-limbic functional connectivity already demonstrated in mood disorders (M. L. Phillips et al., 2008; Rive et al., 2013). These tracts did not appear to be affected in unipolar depression, but were present in the conjunction analysis. Based on this, an explorative analysis in unipolar depression using a more liberal threshold ($p < .01$) revealed that a smaller reduction in FA in this region is indeed present, suggesting that the lack of effect in our original analysis may be attributable to insufficient power to detect an effect of this size. Nevertheless,

aberrant connectivity in the uncinate fasciculus may be more prominent in bipolar disorder and is worthy of further exploration.

The comparison between unipolar and bipolar disorders indicated that reduced white matter integrity in the left posterior cingulum specifically characterizes bipolar disorder, suggesting reduced structural connectivity in this area. A number of studies support the importance of the posterior cingulum in neurocognitive functions such as memory, attention and planning (Delano-Wood et al., 2012; Kantarci et al., 2011). Although a degree of cognitive decline has been described in both unipolar and bipolar disorders (Daniel et al., 2013; G. Xu et al., 2012) there is increasing evidence suggesting that cognitive deficits might be more representative of bipolar disorder (Maalouf et al., 2010; G. Xu et al., 2012). The measured reduction of FA in this area in bipolar patients supports the possibility that abnormalities in the white matter of the posterior cingulum might contribute to the observed impairment present in this diagnostic group. However it is important to mention that we did not have access to cognitive measures from the primary studies and this interpretation remains speculative. Moreover the only DTI study to date that directly compared unipolar and bipolar patients with DTI reported reduced FA in the right posterior superior longitudinal fasciculus and in the inferior parietal cortex in bipolar patients (Versace et al., 2010b), confirming that the strength of the findings in the cingulum white matter requires further direct testing. We also found reduced FA in the right anterior superior longitudinal fasciculus, but this area was not present in either our comparison or conjunction analyses and so we cannot conclude that white matter integrity in this region either does or does not differ between conditions.

TBSS studies showed greater reductions in FA in the areas where differences were measured. Group comparisons in VBA approaches rely on correct and comparable

alignment of individual scans in both groups to a template to locate differences in FA. Anatomical differences between groups may contribute to white matter tract misalignment between groups, affecting group FA comparisons (S. M. Smith et al., 2006). In comparison, TBSS uses a further step whereby FA values are projected on to a skeleton of known nearby tracts, limiting problems caused by misalignment between groups. Smith et al (S. M. Smith et al., 2006) noted the particular relevance of this effect in case of comparison with diseased samples with enlarged lateral ventricles. In this case VBA analysis might overestimate the level of FA in the anterior corpus callosum when compared with TBSS. As there is some evidence of ventricular enlargement in affective disorders (Arnone et al., 2009; Kempton et al., 2011) and the regions where differences were detected are in close proximity to the lateral ventricles, this mechanism might have contributed to the differences measured between TBSS and VBA in the analysis. In this context TBSS might provide a more accurate estimate at least in some of the white matter tracts running close to the ventricular system.

We also examined clinical and demographic moderators of our main results using meta-regressions, which showed that in bipolar disorder, studies with older patient samples found smaller reductions in FA in the left cingulum. A speculative interpretation of this effect might be that long-term treatment ameliorates deficits in this area. Unfortunately we were unable to adequately test whether illness duration (which might provide a proxy index of treatment duration) was a significant moderator as many studies did not report this. Alternatively, later onset affective disorders may have somewhat different neurobiological correlates than the more common earlier onset variants. It is important to note however that meta-regressions are exploratory and should be interpreted with caution, as they do not directly test relationships within samples.

Results of this meta-analysis provide strong evidence for the presence of white matter microstructural alterations in both unipolar and bipolar disorders. The degree of anisotropy present in a tissue is known to be dependent on the presence of axonal membranes, but the exact cause of variations in anisotropy is not fully understood (Beaulieu, 2002). One possible interpretation is that reductions in FA are expression of demyelination. Investigation of demyelination would be best complemented with other measures of anisotropy such as radial diffusivity (RD), commonly increased in the presence of demyelination, and axial diffusivity, which is often unchanged in the same context (Song et al., 2002). It was not possible to include these measures in this meta-analysis as few studies reported these values. However RD is generally found to be increased in areas that show reduced FA (Benedetti, Yeh, et al., 2011; Korgaonkar et al., 2011; Murphy et al., 2012), suggesting that findings presented in this meta-analysis may be due to demyelination. The presence of white matter hyperintensities, associated with demyelination, in bipolar disorder (Kempton et al., 2008) provides further support for this. However there is also some evidence suggesting that abnormalities in axonal organization might contribute to alterations in FA although in brain regions outside the corpus callosum (Cole et al., 2012).

Our results should be interpreted with some caution due to limitations inherent to meta-analyses. One such limitation is publication bias. Although we did not find any direct evidence for this in our analyses it is not possible to exclude small study bias (Arnone, McIntosh, et al., 2012), such that smaller studies with large effects are more likely to be published and to contribute to the results. Other limitations include the reliance on peak coordinates provided in published papers, which do not provide as much detail as individual-level data or statistical parametric maps (Selvaraj et al., 2012). However these are challenging to obtain and in their absence this method is still capable of producing reliable results (Radua et al., 2012). Including statistical

maps is likely to increase sensitivity of meta-analyses sand the sharing of maps through online repositories such as Neurovault would make it simpler to include them in future analyses (Gorgolewski et al., 2014).

A further limitation is the difference in mood state of depressed and bipolar patients. The majority of patients with depression were currently depressed at the time of scanning while the majority of bipolar disorder participants were euthymic, and the limited number of studies in each category prevented statistical analysis of mood state effects. It is not possible to exclude the contribution of mood 'state' to the findings, although it is plausible to think that brain structure would be more stable. Nevertheless further research investigating the contribution of mood state to neuroimaging findings is warranted as there is very little data available in the literature (Arnone et al., 2013; Arnone, McKie, Elliott, Thomas, et al., 2012). Zanetti and colleagues (Zanetti et al., 2009) for instance found several areas of reduced FA in depressed bipolar patients vs. remitted individuals in areas outside the regions identified in this meta-analysis and the only study investigating mood state within DTI measures in depression was conducted in late life depression (W. D. Taylor et al., 2011).

It is also noteworthy that whilst patients with depression were largely medicated with antidepressants or unmedicated, the majority of patients with bipolar disorder received mood stabilizers or antipsychotics. It is difficult to estimate the potential contribution of pharmacological treatment in relation to the results, for instance medication may ameliorate alterations in white matter related to the disease process, potentially concealing differences (Arnone et al., 2013). We did not find any robust effect of lithium exposure in our meta-regressions. Because of the inconsistent reporting of lithium use in the included studies, it is possible that our meta-regression had insufficient power to detect any such effect.

Clinical details were often insufficiently reported in the studies for comprehensive and powerful subgroup or meta-regression analyses. Including a range of clinical variables in future neuroimaging studies would benefit future meta-analyses greatly. Relevant clinical information could include bipolar subtype (e.g. I/II), mental state at the time of scanning, rating scale scores, medication status, type of medication administered (e.g. lithium) and duration of administration, details of co-morbidities, age of onset/duration of illness, and number of episodes.

Furthermore, given that between diagnoses comparisons were based on spatial effect size maps from unipolar and bipolar patients relative to controls acquired in different studies, with the available level of details in individual studies, it is not possible to be sure that the bipolar and unipolar samples were comparable in all relevant clinical variables. Future studies directly comparing bipolar with unipolar patients would allow better matching and controlling for these clinical variables, and could more accurately elucidate the potential effects of these variables on neuroimaging findings.

There may also be alternative techniques aside from conjunction analyses to investigate common changes in the unipolar and bipolar samples, such as combining samples to identify common changes, although this may result in measuring effects present in only one of the disorders with an enhanced effect size.

In conclusion, results from this meta-analysis support the presence of reduced white matter integrity in the genu of the corpus callosum in affective disorders and in the left cingulum white matter in bipolar disorder only. TBSS methods might be more sensitive to these deficits than other whole brain methods including VBA or older approaches such as measurement of corpus callosum area (Arnone et al., 2008; Arnone, McIntosh, et al., 2012). Although the exact underlying cause of these white

matter microstructural changes remains to be elucidated, findings are consistent with the involvement of brain circuitry known to be affected in mood disorders.

## 3.5 Supplementary material

To allow combination of VBA and TBSS studies the TBSS template included in AES-SDM (Peters et al., 2012) was adopted. The TBSS template is based on the FMRIB58 FA skeleton (http://www.fmrib.ox.ac.uk/fsl). This is a 3D map of the main white matter tracts in the brain, created by taking the areas of highest FA from an average of diffusion-weighted images from 58 subjects. The use of this skeleton in AES-SDM restricts the analysis to the same white matter tracts available in TBSS analyses. In this model results from VBA studies are only analyzed when they fall within the same areas used by TBSS studies.

Heterogeneity analyses, using the Q statistic, were also performed with AES-SDM, and followed up with meta-regressions to understand sources of variability among studies, as described previously (Radua et al., 2012; Radua & Mataix-Cols, 2009). Any areas of significant heterogeneity, which overlapped with our main findings, were explored using meta-regressions. We considered the following variables in meta-regressions: age, sex, illness duration, depression severity and proportion of patients taking medication. To facilitate assessment of severity, Montgomery-Depression Rating Scale scores were converted to HAMD-17 equivalents (Heo, Murphy, & Meyers, 2007).

| Area | MNI Coordinates | SDM *Z*-Value | *P*-Value | Number of Voxels |
|---|---|---|---|---|
| **MDD > HC** | | | | |
| No significant clusters | | | | |
| **MDD < HC** | | | | |
| Genu of corpus callosum/forceps minor | -6, 26, 10 | -2.10 | < .001 | 259 |
| R cerebellum[1] | 20, -54, -22 | -1.53 | < .001 | 155 |
| L superior longitudinal fasciculus[2] | -36, -38, 24 | -1.34 | < .001 | 48 |
| L anterior thalamic radiation/forceps minor/inferior fronto-occipital fasciculus/uncinate fasciculus[3] | -16, 44, -12 | -1.14 | 0.002 | 12 |
| **BD > HC** | | | | |
| R superior longitudinal fasciculus[4] | 40, 0, 30 | 1.03 | < .001 | 49 |
| **BD < HC** | | | | |
| L cingulum | -12, -36, 38 | -2.72 | < .001 | 325 |
| L genu of corpus callosum (forceps minor)/anterior thalamic radiation/ cingulum/inferior fronto-occipital fasciculus/uncinate fasciculus | -8, 32, 4 | -2.06 | < .001 | 241 |
| R posterior inferior fronto-occipital fasciculus/inferior longitudinal fasciculus[5] | 34, -60, 4 | -1.73 | < .001 | 24 |
| R anterior inferior fronto-occipital fasciculus | 30, 26, 16 | -1.62 | < .001 | 26 |
| R corticospinal tract/superior longitudinal fasciculus[6] | 28, -14, 30 | -1.37 | .003 | 17 |
| **MDD > BD** | | | | |
| L cingulum | -16, -34, 34 | 2.77 | < .001 | 159 |
| **MDD < BD** | | | | |
| R cerebellum[7] | 24, -56, -24 | -1.07 | < .001 | 52 |
| **MDD = BD** | | | | |
| L genu of corpus callosum | -6, 28, 10 | -1.46 | < .001 | 269 |

**Table 3-3. Regions of significant differences in fractional anisotropy between patients with MDD and BD vs. HC and MDD vs. BD. BD, bipolar disorder; HC, healthy controls; MDD, major depressive disorder; MNI, Montreal Neurological Institute; SDM, signed differential mapping; L, left; R, right.This table provides details of all significant clusters, regardless of whether they met our criteria for reliability and robustness. Results that met criteria for robustness are described in the manuscript. Jackknife analysis, visual inspection of funnel plots, and publication bias analyses indicated that the following clusters were not reproducible and robust: MDD: [1]driven by only two studies, Jia *et al.* (5) and Tha *et al.* (6); [2]driven by two studies, Jia *et al.* (5) and Zou *et al.* (7); [3]not statistically significant after Guo *et al.* (8), Jia *et al.* (5), Peng *et al.* (9) and Ouyang (10) were excluded. BD: [4]driven only by Mahon *et al.* (11); [5]not significant when Chaddock *et al.* (12) and Lu *et al.* (13) were excluded, and a funnel plot showed evidence of publication bias in this cluster, which was supported by a significant Egger's test ($z$ = -2.71, $p$ < .01);[6]no longer significant when Cui *et al.* (14) and Lagopoulos *et al.* (15) were excluded; [7]driven by two studies, Jia *et al.* (5) and Tha *et al.* (6).**

# 4 Common and Distinct Patterns of Grey Matter Volume Alteration in Major Depression and Bipolar Disorder: Evidence from Voxel-Based Meta-Analysis

*As published in Molecular Psychiatry (Wise, Radua, Via, et al., 2016). Supplemental material accompanying the paper is presented at the end of the chapter.*

## 4.1 Introduction

Affective disorders such as major depression (MDD) and bipolar disorder (BD) are serious conditions that significantly affect quality of life (Kessler et al., 2003; Merikangas et al., 2007). In the absence of a definitive understanding of the neuropathology underpinning these disorders, no clinical biomarkers are currently available to aid diagnosis and treatment (K. Botteron et al., 2012; Fu & Costafreda, 2013; Wise et al., 2014). This is a particularly significant issue given the frequency of misdiagnosis and inappropriate treatment in affective disorders (Angst et al., 2011). As a result, biomarker discovery and optimisation are essential steps for future progress.

Neuroimaging studies have identified a number of differences between patients with affective disorders and healthy individuals in brain volume, function, neurochemistry, and connectivity in key neurobiological circuits involved in mood regulation (Arnone et al., 2016; Arnone, Mumuni, Jauhar, & Cavanagh, 2015; Kempton et al., 2008; Price & Drevets, 2012; Wise et al., 2015, 2014). Grey matter volume changes in affective disorders have been well documented in a number of cortical and subcortical structures including prefrontal regions and the hippocampus (Arnone, McIntosh, et al., 2012; Kempton et al., 2011, 2008; Selvaraj et al., 2012). It is at present unclear to what extent specific or common morphological alterations occur in MDD and BDs

given the paucity of direct comparisons and inconsistencies in the available findings. The two studies that have addressed this issue have identified differences in prefrontal regions; however, the precise location differs in these studies (de Azevedo-Marques Périco et al., 2011a; Redlich et al., 2014). Gaining a more detailed insight into the neuropathological relationship between these disorders is an essential step in providing a more precise definition of candidate diagnostic biomarkers at the brain level, which could improve current classifications of affective disorders.

The aim of this meta-analysis was to use the largest database of voxel-based morphometry (VBM) studies in affective disorders to date by taking advantage of a thorough and detailed meta-analytic technique to 1) identify morphometric changes in MDD and BD compared to healthy controls and 2) compare results across diagnostic groups to assess morphometric differences and similarities that may reflect common and/or distinct neuropathological pathways in affective disorders. Most importantly, we adopt an improved meta-analytic technique with increased sensitivity, specificity, and reliability of the analyses, by combining statistical maps from some of the original studies with peak coordinates conventionally used in neuroimaging meta-analyses.

## 4.2 Methods

### *4.2.1 Literature searches*

We searched Pubmed, Scopus and ScienceDirect for studies comparing patients with MDD or BD with control groups published up to January 2015 using the following keywords: Magnetic resonance imaging OR MRI AND depression OR BD OR mania OR mood disorders. Broad search terms were used to minimize the likelihood of missing any relevant studies. Reviews and meta-analyses were cross-referenced to identify

studies which were missed in the literature searches. Authors were contacted for unpublished data including t-maps from the original studies. A systematic approach compliant with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(Moher et al., 2009) was adopted.

Studies were excluded if: 1) adopted neuroimaging techniques other than MRI whole-brain voxel-based morphometry; 2) participants age was below 18 or above 65 (to minimize the effect of neurodevelopment and neurodegeneration, respectively); 3) samples were confounded by any comorbid neurological conditions; 4) t-maps were unavailable, consistent statistical thresholds throughout the brain were not used or peak coordinates were not reported; 5) included ≤10 patients. If the same patient group was used in multiple studies, only the study with the largest sample was included. Conversely, when the same control group was used in several subgroup comparisons, only a combined summary result was included in the meta-analysis (see supplemental methods for details). For studies that used longitudinal treatment designs, only baseline pre-treatment data were included.

### *4.2.2 Meta-analysis*

Meta-analysis was performed using the anisotropic effect size version of Seed-based *D* Mapping (formerly Signed Differential Mapping, AES-SDM) (Radua et al., 2014). This method has been described in detail elsewhere (Radua et al., 2012; Radua & Mataix-Cols, 2009). In summary, AES-SDM allows combination of peak coordinates and statistical parametric maps to create whole-brain effect size and variance maps, which are then used to perform voxel-wise random effects meta-analyses. Although meta-analyses based on peak coordinates alone are able to produce reliable results, the addition of original statistical maps substantially improves the sensitivity of the analyses (Radua et al., 2012). AES-SDM allows meta-analytic summaries of grey

matter volumes within each disorder (e.g. MDD and BD vs. healthy controls) and comparisons of abnormalities between conditions (e.g., depression vs. BD) based on the evaluation of effect sizes. Finally, the multimodal analysis function of the AES-SDM statistical package allows conjunction analyses to be performed, which enabled us to identify regions where both patient groups show common differences with respect to controls, while taking into account error in the estimation of the magnitude of these differences (Radua et al., 2013).

AES-SDM also allows heterogeneity to be systematically quantified in a voxel-wise manner using the Q statistic. The overlap between significant areas of heterogeneity with areas of grey matter differences was systematically investigated with separate simple meta-regressions using available potential confounders where these were provided in a sufficient proportion of the included studies. Given the relatively small number of studies, we set the cut-off for inclusion of potential confounders in meta-regressions to ≥ 20 studies in order to minimize the occurrence of false positives (Higgins & Thompson, 2004). For MDD, we conducted meta-regressions with antidepressant medication use, depression duration (from age of onset), depression severity, mean patient age, and sex. For BD, we used mood state, depression duration, antipsychotic medication use, lithium use, mean patient age, and sex. We also examined effects of magnetic field strength and image smoothing level for both conditions. Studies that did not report these measures were excluded from these analyses. To enable meta-regressions to be conducted using a consistent measure of depression severity, when studies reported Montgomery-Åsberg Depressing Rating Scale (Montgomery & Asberg, 1979) scores, these were converted to Hamilton Depression Rating Scale (M. Hamilton, 1960) equivalents using the method devised by Heo and others (Heo et al., 2007). Group differences in demographic and clinical

variables were explored to discover any potential confounders in group comparisons by using standard meta-analytic tests weighted by sample size.

Significant clusters were tested for publication bias using funnel plots and Egger's test on effect size estimates extracted from the cluster peak, performed using the Metafor package (Viechtbauer, 2010) for R (http://www.rproject.org). Funnel plots of effect sizes in each cluster were also visually inspected to ensure that results were robust. Finally we assessed reliability of our meta-analytic results with a jack-knife analysis, in which the meta-analysis is rerun iteratively with each study left out in one iteration. This method assesses the reliability of significant results, on the assumption that reliable results should be robust to the removal of individual studies, and should therefore remain present in the majority of jack-knife iterations. Clusters that were no longer significant in the meta-analysis in 10% or more of the iterations were rejected as we wished to include the most robust results, which should be present in the vast majority of jack-knife iterations. In the text we only report clusters that met our criteria for robustness. We provide full results and details regarding the meta-analysis method in supplemental methods.

## 4.3 Results

### *4.3.1 Literature searches*

Literature searches produced 14,951 results, of which 66 studies met criteria for inclusion (Figure 4-4). We also identified five studies from previous meta-analyses and reviews. In addition, we had access to statistical maps from two unpublished studies, one in MDD and the other in BD. This resulted in a total of 73 studies included in the final analysis. Details are presented in Table 4-4 and Table 4-5.

### *4.3.2 Study characteristics*

#### 4.3.2.1 MAJOR DEPRESSION

We identified 41 studies that included 50 comparisons between patients and healthy controls (Table 4-4), of which statistical maps were available for nine. These studies included a total of 1736 patients and 2365 healthy controls. Patients' mean age was 38.5 years (SD=9.7) and 38.7% were male. The mean age of healthy control participants was 37.1 years (SD = 7.8), and 39.5% were male. In studies that provided information on mood state, 1348 patients (94%) experienced symptoms of depression at the time of scanning and 88 (6%) were euthymic.

Demographic details were well reported across studies (41 studies, 98%). With regard to clinical information, eleven studies (26%) did not mention depression severity and 7 (17%) did not refer to duration of illness.

#### 4.3.2.2 BIPOLAR DISORDER

We identified 32 studies with 36 comparisons between patients and healthy controls (Table 4-5), representing a total of 980 patients and 1427 controls. Original statistical maps were available for 6 of these studies. Demographic details were reported in all studies. Availability of clinical information was less consistent with 8 studies (25%) not reporting the number of medicated patients, and 11 (34%) not providing treatment details. With regard to symptoms, 9 (28%) studies did not report the mood state, 17 studies (53%) did not provide a measure of depressive symptoms, 16 studies (50%) did not provide information on manic symptoms, 3 studies (9%) did not provide a measure of illness duration, and 18 (56%) did not provide information on symptoms severity. The mean age of patients was 37.6 years (SD = 4.4) and 44.1% were male. The mean age of controls was 35.9 years (SD = 4.8), and 43.8% were male. In relation to sub-types, 808 patients (82%) experienced type I disorder, 91 (9%) were diagnosed

as type II, and for 81 patients (8%) this information was not available. In the studies that provided details of mood state, 438 patients (56%) were euthymic at the time of scanning, 218 (28%) experienced symptoms of depression, 118 (15%) were manic and 5 (1%) had mixed symptoms.

#### 4.3.2.3 MAJOR DEPRESSION VS. BIPOLAR DISORDER

Studies in MDD and BD included patients of similar ages (omnibus test $Q_M^{(1)} = .28$, $p = .60$) and sex ($Q_M^{(1)} = .95$, $p = .33$). Studies which reported duration of illness suggested shorter total durations of illness in patients with MDD than BD (weighted means 8.1 vs. 12.5 years, $Q_M^{(1)} = 9.51$, $p <= .002$). Predictably, more patients were in a depressive state at the time of scanning in MDD studies ($X^2_{(1)} = 22.30$, $p < .001$).

### *4.3.3 Meta-analysis*

#### 4.3.3.1 MDD VS. HEALTHY CONTROLS

Grey matter volume differences in depression relative to healthy controls are shown in Table 4-1 and Figure 4-1**Error! Reference source not found.**. Clusters that did not meet criteria for robustness are shown in Table 4-6. The largest regions showing smaller grey matter volume in MDD were observed bilaterally in two clusters comprising the insula, extending into the posterior part of the inferior frontal gyrus and the anterior superior temporal gyrus. The ventromedial prefrontal cortex showed lower volume in a large area which was predominantly inferior to the anterior cingulate cortex. The posterior cingulate cortex and dorsal anterior cingulate cortex also exhibited lower volumes. Several lateral prefrontal regions showed smaller volumes, as did the left inferior parietal gyrus and the right fusiform gyrus. Regions of lower volume were also present in a number of subcortical and medial temporal regions, including the left caudate, left hippocampus and left parahippocampal gyrus.

Regions of greater volume relative to healthy controls were observed in the bilateral superior occipital gyrus, extending into the cuneus. Smaller clusters showing greater volume were found in the right angular gyrus and right postcentral gyrus.

There was no evidence of publication bias or detectable small study effects in any cluster, as indicated by non-significant Egger's tests of funnel plot asymmetry (all $p$ values > .05). Details of brain regions where significant heterogeneity was measured are provided in Table 4-7. Significant between-study heterogeneity was explored with meta-regression analyses. Results of these analyses indicated that studies with lower mean depression severity found smaller grey matter volumes relative to controls in the left hippocampus (peak MNI = -30, -18, -16, $Z$ = 2.73, $p$ < .001, 40 voxels), studies with a smaller proportion of men found smaller grey matter volume compared with controls in bilateral ventromedial prefrontal cortex (peak MNI = 0, 38, -18, $Z$ = 2.17, $p$ < .001, 359 voxels), and studies with older patients found smaller volumes relative to controls in the left insula (peak MNI = -42, 16, -2, $Z$ = -2.73, $p$ < .001, 49 voxels; Figure 4-1). We found no association with antidepressant medication use or depression duration. When examining methodological variables, studies using higher field strength scanners showed smaller volumes relative to controls in the left superior temporal gyrus (peak MNI = -50, 0, -2, $Z$ = -2.53, $p$ < .001, 40 voxels), while the opposite pattern was observed in the ventromedial PFC (peak MNI = -2, 40, -18, $Z$ = 2.0, $p$ < .001, 187 voxels; Figure 4-1**Error! Reference source not found.**).

#### 4.3.3.2 BIPOLAR DISORDER VS. HEALTHY CONTROLS

Patients with BD differed from healthy controls in grey matter volume in a number of regions (Table 4-2, and Figure 4-1). Clusters that did not meet criteria for robustness are shown in Table 4-8. The largest areas showing lower grey matter volume in patients relative to controls were in the bilateral insula and superior temporal gyrus.

Another large cluster where smaller volumes were observed was located in the medial prefrontal cortex, including the anterior cingulate cortex. We also found small areas showing greater volume relative to controls in a number of areas, including a number of cerebellar regions, bilateral middle frontal gyrus, right middle and inferior temporal gyrus, and right middle occipital gyrus.

Egger's test of funnel plot asymmetry did not identify any evidence of publication bias in any cluster (all $p$ values $> .05$). A number of regions showed significant between-study heterogeneity (Table 4-9). Meta-regression analyses revealed that smaller volumes relative to controls were associated with increasing age in the right middle temporal gyrus (Figure 4-1, peak MNI = 62, -26, -6, $Z$ = -3.07, $p < .001$, 186 voxels). Patient age was also associated with smaller volumes compared with controls in the right caudate (Figure 4-1, peak MNI = 8, 14, 12, $Z$ = -2.60, $p < .001$, 55 voxels). We found no significant associations with mood state, antipsychotic medication use, lithium use, sex, or methodological variables.

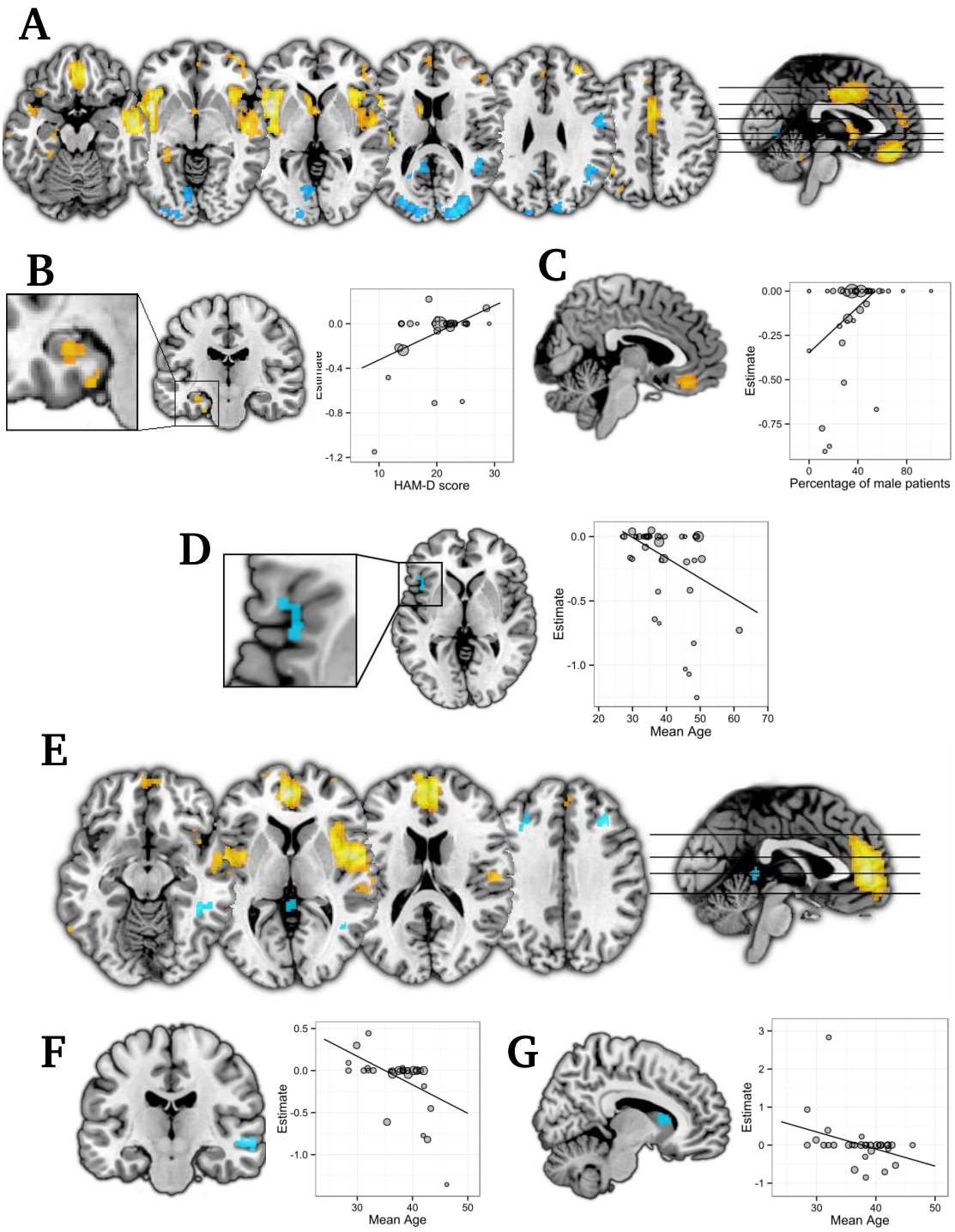


Figure 4-1. A) Results of MDD meta-analysis. B) Results of meta-regression with depression severity in MDD. C) Results of meta-regression with sex in MDD. D) Results of meta-regression with patient age in MDD. E) Results of BD meta-analysis. F, G) Results of meta-regressions with age in BD. Orange represents lower volume in patients relative to controls or positive relationships with regressors in meta-regressions, blue represents greater volume relative to controls or negative relationships with regressors. In meta-regression plots, point size represents study weights. All images are shown in neurological convention; left on the image corresponds to left in the brain. Effect sizes represent effect sizes at the peak of the cluster.

| Peak MNI Coordinate | *Z* | P | Voxels | Brodmann Areas | Regions |
|---|---|---|---|---|---|
| **MDD < Healthy Controls** | | | | | |
| -42,8,-2 | 4.05 | <0.001 | 3258 | 22, 38, 48 | Left insula, inferior frontal gyrus, temporal pole, superior temporal gyrus |
| 54,-8,-14 | 4.00 | <0.001 | 1912 | 21, 22, 48 | Right superior temporal gyrus, Insula, inferior frontal gyrus |
| -2,40,-18 | 3.40 | <0.001 | 908 | 11 | Left gyrus rectus, left medial orbitofrontal cortex, anterior cingulate cortex |
| 0,4,42 | 3.34 | <0.001 | 729 | 24/23 | Left middle cingulate cortex |
| -10,16,6 | 3.53 | <0.001 | 320 | 25 | Left caudate nucleus |
| 44,48,-8 | 3.12 | <0.001 | 282 | 46, 47 | Right middle frontal gyrus, orbital part |
| 32,42,30 | 3.10 | <0.001 | 144 | 46 | Right middle frontal gyrus |
| -28,-38,-4 | 2.88 | 0.001 | 104 | 37 | Left hippocampus, parahippocampal gyrus |
| -40,-54,46 | 3.21 | <0.001 | 93 | 40 | Left inferior lobule |
| 44,-24,-24 | 2.78 | 0.001 | 92 | 20 | Right fusiform gyrus |
| 4,48,22 | 2.80 | 0.001 | 53 | 32 | Right anterior cingulate cortex |
| -20,-18,-18 | 2.73 | 0.001 | 41 | 35 | Left hippocampus, parahippocampal gyrus |
| -4,36,40 | 2.67 | 0.001 | 36 | 32 | Left superior medial frontal gyrus |
| **MDD > Healthy Controls** | | | | | |
| 26,-90,14 | -1.81 | ~0 | 731 | 17, 18 | Right Superior occipital gyrus, cuneus, middle occipital gyrus |
| -10,-96,12 | -1.03 | <0.001 | 733 | 17, 18 | Left superior occipital gyrus |
| 44,-50,26 | -1.33 | <0.001 | 457 | 39 | Right angular gyrus, middle temporal gyrus |
| 52,-4,26 | -1.25 | <0.001 | 161 | 4 | Right postcentral gyrus |

**Table 4-1. Clusters showing differences between MDD and controls that met our criteria for robustness**

| Peak MNI coordinate | *Z* | P | Voxels | Brodmann Areas | Regions |
|---|---|---|---|---|---|
| **BD < Healthy Controls** | | | | | |
| -4,50,4 | 4.04 | <0.001 | 2210 | 10, 32 | Bilateral anterior cingulate cortex, superior & ventral medial prefrontal cortex |
| 54,2,0 | 3.95 | <0.001 | 1898 | 21, 22, 38, 48 | Right temporal pole, superior temporal gyrus, right insula |
| -48,-2,0 | 3.06 | <0.001 | 436 | 48 | Left superior temporal gyrus, left insula, left rolandic operculum |
| **BD > Healthy Controls** | | | | | |
| 4,-44,-12 | -1.56 | <0.001 | 158 | 20, 21, 37 | Inferior temporal gyrus, middle temporal gyrus |
| 24,-36,-38 | -1.59 | <0.001 | 127 | - | Middle cerebellar peduncles |
| 34,26,36 | -1.73 | <0.001 | 84 | 46 | Right middle frontal gyrus |
| -32,22,38 | -1.41 | 0.001 | 71 | 46, 9 | Left middle frontal gyrus |
| 2,-38,6 | -1.54 | 0.001 | 54 | - | Cerebellar vermis |
| 38,-78,8 | -1.35 | 0.001 | 15 | 19 | Right middle occipital gyrus |

**Table 4-2. Clusters showing differences between BD and controls that met our criteria for robustness**

| Peak MNI Coordinate | *Z* | P | Voxels | Brodmann Areas | Regions |
|---|---|---|---|---|---|
| **MDD < BD** | | | | | |
| 34,30,40 | -2.46 | <0.001 | 102 | 9, 46 | Right middle frontal gyrus |
| -26,-38,-2 | -2.47 | <0.001 | 74 | 37 | Left hippocampus, parahippocampal gyrus |
| 42,-26,-22 | -2.33 | <0.001 | 72 | 20 | Right inferior temporal gyrus, fusiform gyrus |
| -40,-52,44 | -2.25 | <0.001 | 31 | 40 | Left inferior parietal lobule |
| 4,-42,-22 | -2.10 | <0.001 | 14 | - | Right cerebellar vermis |
| **Reductions in both MDD and BD** | | | | | |
| 52,-4,2 | 4.97 | <0.001 | 753 | 48 | Right superior temporal gyrus, ir |
| -42,0,-2 | 4.69 | <0.001 | 377 | 38, 48 | Left insula, superior temporal gy |
| -4,54,18 | 4.28 | 0.001 | 115 | 10, 32 | Left superior medial frontal gyru cingulate cortex |
| 4,48,22 | 4.20 | 0.001 | 50 | 32 | Right anterior cingulate cortex |

**Table 4-3. Clusters showing similar and different grey matter changes in MDD and BD**

#### 4.3.3.3 MAJOR DEPRESSION VS. BIPOLAR DISORDER CONTRAST

Major depression differed from BD with respect to grey matter volume alterations in several regions (Table 4-3, and Figure 4-2). The most substantial difference involved the right middle frontal gyrus, where smaller grey matter volume relative to controls was specific to MDD. A similar pattern was found in the left hippocampus, right inferior temporal gyrus, left inferior parietal lobule, and right cerebellar vermis. There were no regions in which the opposite pattern was observed.

#### 4.3.3.4 GREY MATTER VOLUME ALTERATIONS COMMON TO BOTH DISORDERS

Conjunction analysis indicated that several regions in the bilateral insula and in the dorsomedial and ventromedial prefrontal cortex, including the pre-genual anterior cingulate cortex, showed smaller volume compared with controls in both conditions (Figure 4-2). No regions showed greater volume compared to controls in both conditions.

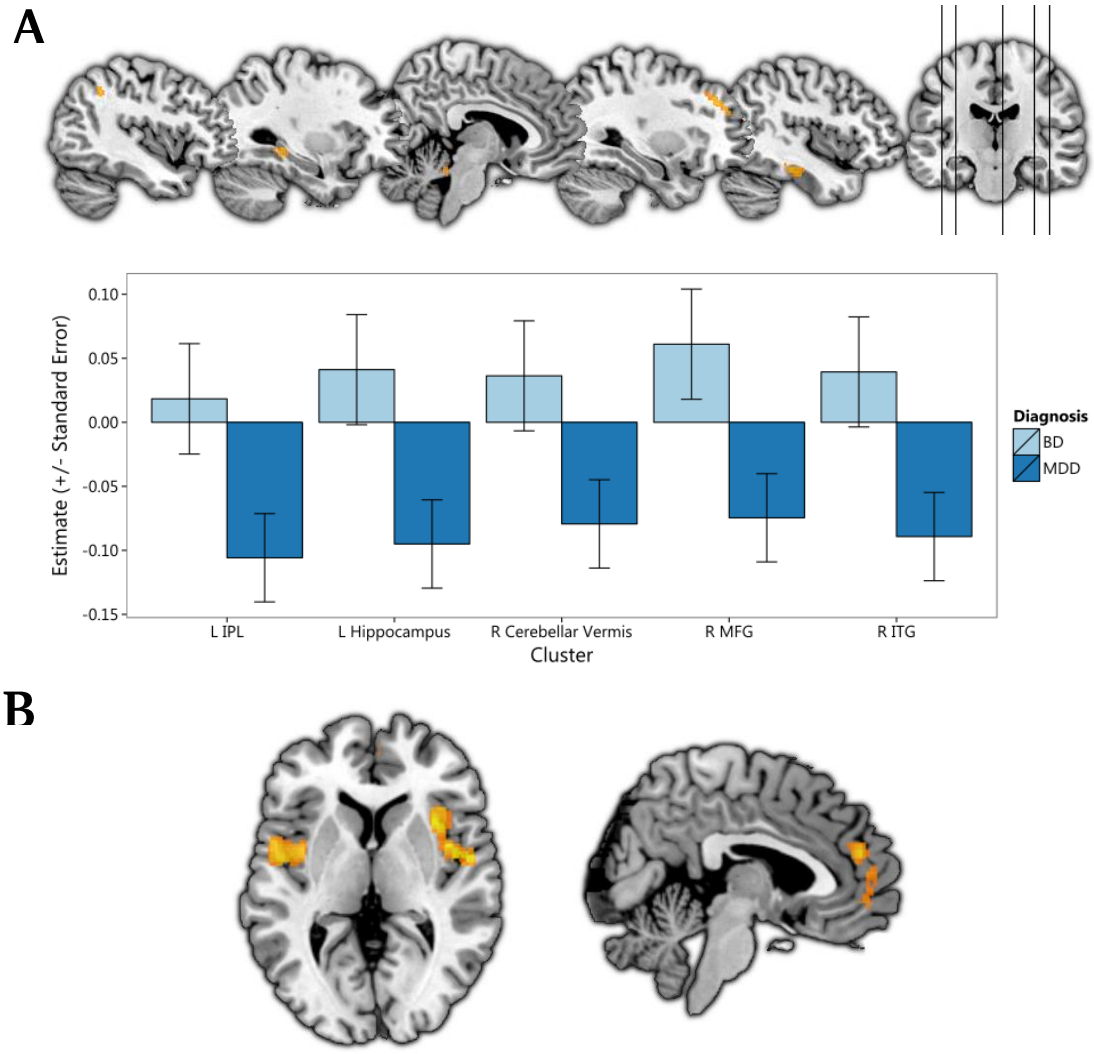


Figure 4-2. A) Regions showing differences between MDD and BD. Orange clusters represent smaller grey matter volume than controls, which is more substantial in MDD. B) Results of the conjunction analysis showing regions with similar volumetric alterations in both conditions. Here orange represents regions showing significantly lower volume in both conditions relative to controls. L = left, R = right, IPL = Inferior Parietal Lobule, MFG = Middle Frontal Gyrus, ITG = Inferior Temporal Gyrus. Effect sizes represent effect sizes at the peak of the cluster.

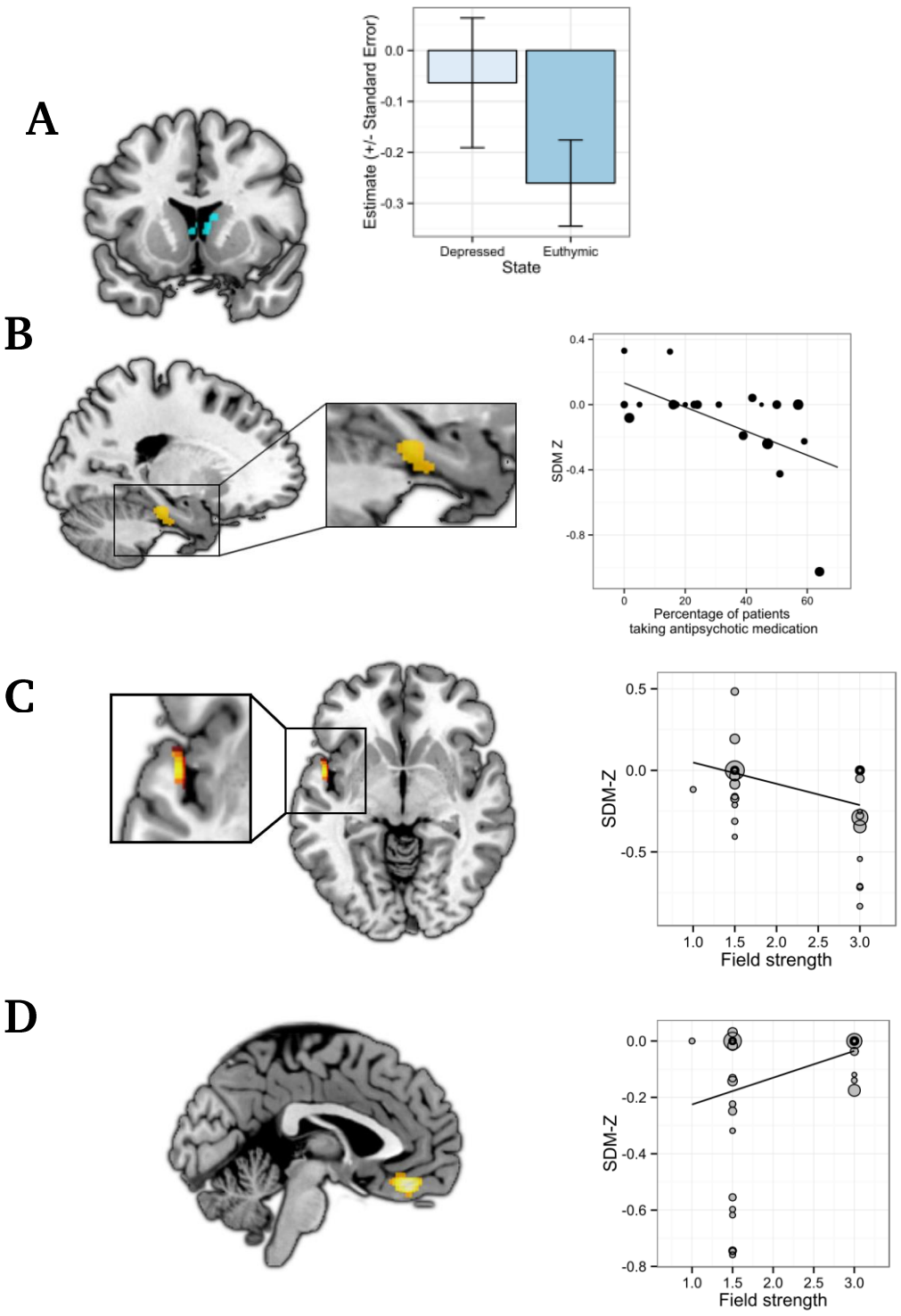


**Figure 4-3. A) Results of mood state comparison in bipolar disorder. B) Results of meta-regression with antipsychotic medication load in bipolar disorder. C & D) Results of meta-regression with scanner field strength in major depression.**

## 4.4 Discussion

In this paper we report findings from the largest meta-analysis conducted to date of voxel-based morphometry studies in MDD and BD. We compared results from these two conditions to identify common and distinct patterns of grey matter volume alterations. We showed that the two conditions share similar patterns of lower volume in the bilateral insula and medial prefrontal cortex, suggesting that there may be an underlying pathological mechanism that is common to affective disorders. A number of regions, including the left hippocampus and right dorsolateral prefrontal cortex, differed between conditions, indicating that these disorders may be associated with spatially distinct patterns of pathophysiology.

Both conditions showed smaller grey matter volumes relative to control groups in the medial prefrontal systems, including the anterior cingulate cortex. In MDD this was predominantly located in the most ventral and dorsal regions of the medial PFC, while in BD it was located in a large cluster anterior to the genu of the corpus callosum, although this difference in location was not statistically significant. The conjunction analysis indicated that the volumes of parts of the dorsomedial and ventromedial PFC were robustly lower in both conditions, suggesting a consistent pattern across disorders. These regions have been strongly implicated in mood regulation, and the anterior cingulate cortex in particular has been shown to be crucial in the regulation of affective states (Rive et al., 2013), and has been a target of treatment with deep brain stimulation (Mayberg et al., 2005). Our results are consistent with theories of mood dysregulation in affective disorders that posit that dysfunction in regions such as the medial prefrontal cortex leads to aberrant mood states(M. L. Phillips et al., 2008). Further work is necessary, however, to determine whether the structural differences here are responsible for the altered function of these networks.

We also found that bilateral insula volume was smaller in patents in both conditions. This region is involved in a range of functions, including affective processing and awareness of bodily states (Critchley, Mathias, & Dolan, 2001; Uddin, 2014), and atypical functioning of this region in affective disorders has been found in functional neuroimaging research (J. P. Hamilton et al., 2012; Miller, Hamilton, Sacchet, & Gotlib, 2015). Notably, the insula has also been found by multiple studies to predict treatment response in patients with depression (Fu, Steiner, & Costafreda, 2013; McGrath et al., 2013). Our finding of smaller insular volume in both unipolar and bipolar subjects suggests that structural abnormalities are present in the same areas in which altered function has also been identified. The insula has been implicated in interoceptive processing and general bodily awareness(Craig, 2002), and our results may indicate that structural changes are associated with altered interoceptive function in affective disorders (Avery et al., 2014; Barrett & Simmons, 2015); this is a speculative interpretation, however, that requires direct testing.

Our comparison of the conditions revealed several areas of smaller grey matter volume that were significantly greater in MDD than BD, most prominently in the left parahippocampal gyrus and right dorsolateral prefrontal cortex, specifically the middle frontal gyrus. Smaller volumes of the hippocampus and parahippocampal gyrus have been well documented in MDD, but have been reported less often in BD (Arnone, McIntosh, et al., 2012; Cole et al., 2010; Kempton et al., 2011). Investigators have suggested that this may be due to neuroprotective effects of lithium, which counteracts volume loss in BD (Hajek, Kopecek, et al., 2012). We did not find any significant heterogeneity in the hippocampus in BD, suggesting that there was no variation in effect sizes due to medication or other variables. It is important to note, however, that we cannot exclude the possibility that this may be due to reduced sensitivity of whole brain VBM analyses in small regions such as the hippocampus

(Bergouignan et al., 2009). Additionally, it is unlikely that this difference between conditions can be explained by mood state in MDD given that our meta-regressions showed that lower depression severity in MDD was associated with smaller volumes in this region. Alternatively, this may reflect sparing of the hippocampus in BD due to protective factors in individuals predisposed to the disorder (Ladouceur et al., 2008).

The dorsolateral prefrontal cortex has been linked to emotion regulation (Golkar et al., 2012), and the right dorsolateral prefrontal cortex specifically has been linked to attentional control during emotional tasks (Grimm et al., 2008). Notably, repetitive transcranial magnetic stimulation to this region has been reported to improve symptoms in treatment-resistant depression (Fitzgerald et al., 2006), but results have been less convincing in bipolar depression (Oldani, Altamura, Abdelghani, & Young, 2014). Our results add to this literature by suggesting that volumetric alterations in this region are specific to MDD, indicating that a differential pattern of prefrontal grey matter volume may potentially differentiate these two disorders. It is important to mention that functional alterations have been identified in the right dorsolateral prefrontal cortex in BD (Hassel et al., 2008). The relationship between functional and structural alterations in these conditions remains unclear and further research is essential to understand potential function and/or structural disease-specific alterations within affective disorders in the dorsolateral prefrontal cortex.

Our analyses within each condition also revealed a number of regions of grey matter changes that did not differ significantly in magnitude between disorders but that were not reliably smaller in both disorders relative to controls. One notable difference in MDD compared with controls involved the bilateral occipital cortex, including primary visual and extrastriate cortices, where patients showed a large area of greater volume relative to controls. While a number of studies have highlighted the possibility of

neurochemical (Bhagwagar et al., 2007) and functional (Furey et al., 2015; Keedwell et al., 2009) changes in these regions, this is the first study to identify robust volumetric changes in these regions. Given our efforts to ensure that our results were reliable and robust, it is unlikely that this is simply a false positive produced by the meta-analytic method, although we cannot exclude the possibility that methodological issues in the original studies may have caused spurious results. For example, it is possible this could be an artefact caused by correction for intracranial or total grey matter volume combined with substantially lower grey matter volume in other regions, although this is a speculative interpretation and would require confirmation. The potential role of occipital regions has rarely been investigated in major depression, and further research is required to understand whether these results are robust or whether they are a result of the method used.

We found a number of regions that showed significant between-study heterogeneity, and we explored these using meta-regressions. In MDD, studies with less severely depressed patients showed smaller grey matter volume in the hippocampus than did investigations with more severe patients. This may seem contradictory given that previous studies have showed the opposite pattern (E. S. Brown et al., 2014; Schmaal et al., 2015). It is possible that it may be explained by the use of medication. Treatment with selective serotonin reuptake inhibitors is known to increase hippocampal volume (Arnone, McKie, Elliott, Juhasz, et al., 2012; Frodl et al., 2008), and given this it is possible that more severely depressed patients had received more extensive pharmacotherapy in the past, leading to amelioration of pre-existing grey matter volumetric abnormalities, although we were unable to test this here due to historical treatment data being unavailable in the original studies However it is important to note that we only had access to information regarding current depression severity, and

it possible that lifetime depression severity, or chronic and treatment resistant symptom profiles, may be associated with different neuroanatomical profiles.

Our meta-regression analyses showed effects of demographic variables in both conditions. In MDD, volume of the prefrontal cortex was smaller in studies with fewer male patients. Anatomical differences between sexes have been reported previously in depression (Maller et al., 2014), although it is unclear what drives these differences. In addition we found smaller left insula volumes in studies of MDD with older patients; in contrast, in BD studies with older patients, we found smaller volumes in the right middle temporal gyrus. Thus, there may be a different biological trajectory in affective disorders in relation to these regions, although meta-regressions should be interpreted with caution as they do not directly test relations within samples.

This meta-analysis improves on previous studies in several ways. First, the novel meta-analytic method used here allowed us to identify common and distinct areas of grey matter volume alterations in affective disorders. Given the paucity of reports comparing affective conditions directly, this approach enabled us to identify volumetric aspects of common neuropathological mechanisms, and potentially distinctive biomarkers. Second, we were able to include a larger number of studies due to the rapid growth of the field and our access to as yet unpublished datasets. We are therefore able to provide the most conclusive picture of volumetric changes currently available. Third, we included a number of original statistical maps in our analyses. This substantially improves the sensitivity and specificity of the analysis, especially in cases in which individual studies have small samples (Radua et al., 2012). Finally, the thorough and detailed approach used in this work ensured that findings were robust and that heterogeneity was comprehensively explored. We found no evidence of publication bias or small-study effects; nevertheless, it is important to note

that, given the small sample sizes of the majority of the studies included in the analyses, we cannot exclude the possibility of small-study bias.

Despite these strengths, we should also note several limitations of this meta-analysis. First, we cannot determine causality from these results due to the fact that all the included studies were cross-sectional group comparisons, and it is not clear whether these alterations are part of the pathogenesis of these disorders or a consequence of the illness. It should be noted however that our meta-regressions did not detect any effect of illness duration, providing some evidence against the latter explanation. Second, the effect size comparisons may not provide as accurate a picture of group differences as studies directly comparing the two conditions. To date there have been very few VBM studies directly comparing affective conditions (de Azevedo-Marques Périco et al., 2011a; Redlich et al., 2014) making it difficult to draw firm conclusions concerning potential similarities and differences between disorders. Hence, at present, the approach used in this meta-analysis, with the limitation of indirectly comparing studies' effect sizes, offers the most viable option to reach conclusions generalisable beyond individual studies. Additionally, given the inherent robustness of the meta-analytic method, our results should provide a summary of the most reliable differences between these disorders.

Third, the samples used in the studies differed between disorders with respect to treatment status (e.g., different types of pharmacotherapy). Given that psychotropic medications can have effects on brain structure (Arnone, McKie, Elliott, Juhasz, et al., 2012), it is difficult to be certain that results are not entirely independent from medication status. As a related point, the samples also differed in mood state and illness duration. We found no evidence for effects of these variables in meta-regressions within disorders, suggesting that this is not likely to be a major concern.

However, effects of mood state are particularly difficult to rule out, given that a number of studies included samples of mixed mood states and several did not provide information on mood state. Consequently, it is not possible to comment with certainty on the effect of mood state on our results. Furthermore, we cannot exclude the possibility that undiagnosed cases of BD presented as unipolar depression in the original studies (Angst et al., 2011), and it is not possible to rule out the influence of comorbidities such as anxiety disorders on the results as these were not well described in the original reports. Another concern is that many of the retrieved studies included more controls than patients. Although these unbalanced studies may have theoretically biased results (Scarpazza, Sartori, De Simone, & Mechelli, 2013), it is not clear from the existing literature that this is likely to affect our results and conclusions.

Finally, we cannot be certain that these regions of common grey matter volume alterations are exclusive to affective disorders. A recent meta-analysis (Goodkind et al., 2015) by Goodkind and others found that some of these areas, such as the insula and dorsomedial prefrontal cortex, are lower across a range of psychiatric conditions including affective, anxiety, and psychotic disorders. This suggests that morphometric grey matter changes in these regions are not specifically pathognomonic to affective disorders, or are even a proxy for underlying common disease processes or for risk factors such as life stressors or effects of hormonal or inflammatory changes. Nevertheless the regions identified by Goodkind and others differ from those reported in this meta-analysis in their location and size. For example the authors demonstrated that the anterior left insula extending to the left inferior frontal gyrus was affected across disorders. In our work a more posterior portion of the left insula was shown to be affected in both MDD and BD, which has functional relevance given the anterior-posterior division in insula function, with the poster region being specifically involved in interoception and bodily awareness (Craig, 2002).

In conclusion, we have shown that MDD and BD show a common pattern of lower grey matter volume which predominantly includes the medial prefrontal and insular cortices. In addition, the two conditions also show distinct patterns of volume alterations in a number of other regions, most predominantly the right dorsolateral prefrontal cortex and left hippocampus, which are specific to MDD. There is significant heterogeneity within these results, but this could be partially explained by clinical and demographic differences in clinical samples. These findings suggest targets for neuroanatomical diagnostic biomarkers, but also indicate that affective disorders are more morphologically similar than they are different.

## 4.5 Supplementary material

### *4.5.1 Supplementary methods*

All analyses were conducted using the grey matter template included in AES-SDM using a voxel size of $1mm^3$. We used a significance threshold of $p < .005$ with a peak Z value of >1 and cluster size of >10 voxels for all main analyses. We used a more conservative threshold of $p < .0005$ for meta-regressions as these are more susceptible to false positives, particularly when conducted on a small number of studies[1]. These thresholds have been found to provide the optimal balance of sensitivity and specificity in previous research[2]. As we had a large number of studies in each diagnostic group, we used a less conservative threshold of $p < .001$ for the comparison between MDD and BD. Regions where results were significant in both conditions were submitted to a conjunction analysis to identify regions that were robustly affected in both conditions, accounting for error in the estimation of p-values within individual meta-analyses.To protect against false positives in the conjunction analysis,the threshold was set at $p < .005$ for this analysis, without the correction described by Radua and others in order to test against the conjunction null hypothesis (i.e. no significant

difference in one or fewer disorders) rather than the global null (i.e. no significant difference in any disorder).

### *4.5.2 Supplementary results*

#### 4.5.2.1 RESULTS OF HETEROGENEITY ANALYSIS IN REGIONS WHERE THERE WAS SIGNIFICANT HETEROGENEITY BUT NO MAIN DISORDER EFFECT – BIPOLAR DISORDER

We found that studies with euthymic samples found greater volume reductions in the right caudate than those in other mood states (peak MNI = -4, 10, 4, $Z$ = 2.21, $p$< .001, 120 voxels, Figure 4-3). Although our overall analysis showed no differences between patients and controls here, we performed a subgroup analysis using only studies with euthymic patients and found a cluster of significant volume reductions in the caudate (peak MNI = -6, 14, 0, Z = -3.61, p< .001, 804 voxels), suggesting that this may be specific to the euthymic state.

Meta-regression analysis also revealed that the percentage of patients taking antipsychotic medication at the time of scanning was positively associated with effect size in the left fusiform gyrus and parahippocampal gyrus (peak MNI = -30, -28, -28, $Z$ = --2.20, $p$< .001, 134 voxels), indicating that studies with higher numbers of patients receiving antipsychotic treatment found greater decreases in grey matter volume in this region (Figure 4-3). Again, this region was not present in our main analysis but was present when we conducted a subgroup analysis using only studies with >50% of patients taking antipsychotic medication (peak MNI = -34, -28, -32, $Z$ = 2.01, $p$ = 0.001, 95 voxels). Meta-regression analyses with methodological variables showed that studies with higher strength scanners showed smaller volumes relative to controls in the right caudate (peak MNI = 10, 6, 6, $Z$ = 3.19, $p$< .001, 597 voxels) and the right superior temporal gyrus (peak MNI = 62, -30, 2, $Z$ = 2.57, $p$< .001, 269

voxels). Meta-regression analysis with spatial smoothing level revealed a negative relationship between smoothing level and effect size in the left inferior frontal gyrus (peak MNI = -44, 16, 4, $Z$ = 4.14, $p$< .001, 101 voxels).

All other meta-regression results were non-significant, or did not overlap with regions of heterogeneity.

| Study | Major Depression Patients | | | | | | | Healthy Controls | | | Methods | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | Mean age | Sex (M/F) | Antidepressant % | Duration of illness (y) | State | HAMD-17 | *n* | Mean age | Sex (M/F) | Field strength (Tesla) | Smoothing (mm) |
| Abe et al., 2010 | 21 | 48.1 | 11, 10 | 90 | 6 | 7 Depressed, 2 partially remitted, 12 fully remitted | 9.2 | 42 | 48 | 22, 20 | 1.5 | 6 |
| Amico et al., 2011 | 33 | 32 | 19, 14 | 82 | 3.4 | Depressed | 18.6 | 64 | 30.4 | 36, 28 | 1.5 | 8 |
| Arnone, McKie, Elliott, Juhasz, et al., 2012 | 39 | 36.3 | 12, 27 | 0 | 14.3 | Depressed | 21.8 | 66 | 32.1 | 20, 46 | 1.5 | 8 |
| Arnone, McKie, Elliott, Juhasz, et al., 2012 | 25 | 34.5 | 5, 20 | 0 | 9.4 | Remitted | 0.3 | 66 | 32.1 | 20, 46 | 1.5 | 8 |
| Bergouignan et al., 2009 | 20 | 33.2 | 3, 17 | 100 | 8.5 | Depressed | 23.1 | 21 | 28.2 | 7, 14 | 1.5 | 8 |
| Chaney et al., 2014 | 37 | - | - | - | - | Depressed | - | 46 | - | - | 3 | 10 |
| Cheng et al., 2010 | 68 | 29.9 | 21, 47 | 0 | 11 | Depressed | 22.3 | 68 | 30.5 | 21, 47 | 1.5 | 10 |
| de Azevedo-Marques Périco et al., 2011b | 20 | 29.9 | 5, 15 | 55 | 0.7 | - | 19.6 | 94 | 30.2 | 41, 53 | 3 | 8 |
| Grieve, Korgaonkar, Koslow, Gordon, & Williams, 2013 | 102 | 33.8 | 48, 54 | 0 | 11.3 | Depressed | 21 | 34 | 31.5 | 18, 16 | 3 | 8 |
| Wenbin Guo et al., 2014 | 44 | 27.5 | 22, 22 | 0 | 1.6 | Depressed | 25.2 | 44 | 29.4 | 20, 24 | 1.5 | 10 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Inkster et al., 2011 | 49 | 47.6 | 16, 33 | - | 14.1 | - | - | 183 | 48 | 73, 110 | 1.5 | 10 |
| Inkster et al., 2011 | 96 | 50.4 | 35, 61 | - | 14.5 | - | - | 183 | 48 | 73, 110 | 3 | 6 |
| Jia et al., 2010 | 36 | 34.7 | 20, 16 | 0 | 1.8 | Depressed | 22.3 | 52 | 37.1 | 24, 28 | 3 | 6 |
| Jia et al., 2010 | 16 | 34.2 | 5, 11 | 0 | 6.7 | Depressed | 24.6 | 52 | 37.1 | 24, 28 | 1.5 | 8 |
| Kim et al., 2008 | 22 | 38.5 | 0, 22 | 45 | 17.4 | Depressed | - | 25 | 35.3 | 0, 25 | 1.5 | 8 |
| Klauser et al., 2015 | 56 | 34 | 16, 40 | - | 10.3 | 29 depressed, 27 remitted | - | 33 | 34.7 | 12, 21 | 1.5 | 8 |
| Kong et al., 2014 | 28 | 34.4 | 11, 17 | 0 | 2.11 | Depressed | 21.7 | 28 | 32.1 | 14, 14 | 1.5 | 8 |
| Kroes, Rugg, Whalley, & Brewin, 2011 | 29 | 33.4 | 8, 21 | 76 | - | Depressed | - | 29 | 32.5 | 13, 16 | 3 | 3 |
| Lai, Hsu, & Wu, 2010 | 16 | 37.9 | 5, 11 | 0 | 0.4 | Depressed | 29.1 | 15 | 34.3 | 4, 11 | 3 | 3 |
| Lai & Wu, 2014 | 38 | 36.6 | 18, 20 | 0 | 0.4 | Depressed | 22.3 | 27 | 38.3 | 12, 15 | 1.5 | 8 |
| Lee et al., 2011 | 47 | 46 | 5, 42 | 62 | 3.9 | Depressed | 20.1 | 51 | 45.7 | 5, 46 | 1.5 | 12 |
| Leung et al., 2009 | 17 | 45.5 | 0, 17 | - | 7 | Depressed | - | 17 | 45.8 | 0, 17 | 1.5 | 8 |
| C. Ma et al., 2012 | 18 | 27.4 | 11, 7 | - | 3 | Depressed | 23.9 | 17 | 24.2 | 10, 7 | 1.5 | 8 |
| C. Ma et al., 2012 | 17 | 26.7 | 10, 7 | 0 | 0.22 | Depressed | 25.6 | 17 | 24.2 | 10, 7 | 1.5 | NA |
| Legge et al., 2015 † | 67 | 50.5 | 28, 39 | 67 | 21.8 | Depressed and remitted | - | 67 | 26 | 23, 44 | 1.5 | 8 |
| Machino et al., 2014 | 29 | 39.6 | 16, 13 | 97 | 4.4 | Depressed | 13.9 | 29 | 38.7 | 16, 13 | 1.5 | 8 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Modinos et al., 2014 | 23 | 44.6 | 3, 20 | - | - | - | - | 46 | 25.3 | 32, 14 | 1.5 | 8 |
| Nakano et al., 2014 | 36 | 49 | 14, 22 | - | 5.6 | Depressed & remitted | 15.4 | 54 | 45.4 | 27, 27 | 3 | 8 |
| J. Peng et al., 2011 | 22 | 46.7 | 8, 14 | 23 | 0.7 | Depressed | 19.5 | 30 | 45.9 | 11, 19 | 3 | 8 |
| Hongjun Peng et al., 2014 | 18 | 31.1 | 6, 12 | - | 23.5 | Depressed | 24.1 | 28 | 28.6 | 15,13 | 3 | 12 |
| Hongjun Peng et al., 2014 | 20 | 27.8 | 7, 13 | - | 21.5 | Depressed | 25.6 | 28 | 28.6 | 15,13 | 1.5 | 8 |
| Redlich et al., 2014 | 58 | 37.6 | 22, 36 | - | 11 | Depressed | 22.4 | 58 | 37.7 | 21, 37 | 3 | 8 |
| Rodríguez-Cano et al., 2014 | 32 | 48.7 | 12, 20 | 88 | 11 | Depressed | 21.7 | 64 | 46 | 26, 38 | 1.5 | 4 |
| Salvadore et al., 2011 | 58 | 38.8 | 21, 37 | 0 | 18.4 | Depressed | 20.8 | 107 | 36.2 | 47, 60 | 3 | 11 |
| Salvadore et al., 2011 | 27 | 40.2 | 6, 21 | 0 | 15.1 | Remitted | 0 | 107 | 36.2 | 47, 60 | 3 | 11 |
| Scheuerecker et al., 2010 | 13 | 37.9 | 10, 3 | 0 | 4.4 | Depressed | 16.6 | 15 | 35.5 | 10, 5 | 3 | 8 |
| Serra-Blasco et al., 2013 | 22 | 44 | 7, 15 | - | 0.5 | Depressed | 16.6 | 32 | 46 | 9, 23 | 3 | 8 |
| Serra-Blasco et al., 2013 | 22 | 48 | 2, 20 | - | 17.9 | Remitted | 4 | 32 | 46 | 9, 23 | 3 | 8 |
| Serra-Blasco et al., 2013 | 22 | 49 | 4, 18 | - | 22.7 | Depressed | 21 | 32 | 46 | 9, 23 | 3 | 8 |
| Shah, Ebmeier, Glabus, & Goodwin, 1998 | 20 | 47.7 | 13, 7 | 45 | 1.6 | Remitted | 2.6 | 20 | 49.3 | 13, 7 | 1 | 12 |
| Shah et al., 1998 | 20 | 48.9 | 13, 7 | 100 | 5.5 | Depressed | 20.6 | 20 | 49.3 | 13, 7 | 1 | 12 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Soriano-Mas et al., 2011 | 70 | 61.6 | 29, 41 | 71 | 10.6 | Depressed | 28.6 | 40 | 59.2 | 17, 23 | 1.5 | 12 |
| Sprengelmeyer et al., 2011 | 17 | 45.6 | 8, 2 | 100 | - | Depressed | 23.2 | 21 | 42 | 9, 12 | 1.5 | 8 |
| Stratmann et al., 2014 | 132 | 37.9 | 56, 76 | 94 | 7.8 | Depressed | 20.5 | 132 | 37.8 | 58, 74 | 3 | 8 |
| Treadway et al., 2009 | 19 | 35.2 | 9, 10 | 0 | 12.9 | Depressed | 21.5 | 19 | 30.3 | 9, 10 | 3 | 12 |
| Wagner et al., 2011 | 30 | 0 | 5, 25 | - | 6 | Depressed | 20.1 | 30 | 0 | 5, 25 | 1.5 | 12 |
| Li Wang et al., 2012 | 18 | 34 | 9, 9 | 0 | 0.4 | Depressed | 25 | 18 | 35 | 9, 9 | 3 | 6 |
| Lan Wang et al., 2014 | 13 | 30.9 | 0, 13 | - | - | Depressed | - | 10 | 29.8 | 0, 10 | 3 | 4 |
| Yoshikawa et al., 2006 | 11 | 48.5 | 0, 11 | 0 | - | Depressed | - | 29 | 48.6 | 0, 29 | 1.5 | 8 |
| Zou et al., 2010 | 23 | 31.1 | 10, 13 | 0 | 0.6 | Depressed | 24.4 | 23 | 36.6 | 10, 13 | 3 | 10 |

**Table 4-4. Characteristics of major depression studies included in the meta-analysis. M = male, F = female, y = years, HAMD-17 = Hamilton Depression Rating Scale 17-item, † = unpublished voxel-based morphometry data from the sample reported**

| | Bipolar Disorder Patients | | | | | | | | | | Healthy Controls | | | Methods | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | ***N*** | **Age** | **Sex (M,F)** | **Lithium (%)** | **Antipsychotic medication (%)** | **Duration of illness (y)** | **Subtype** | **State** | **HAMD-17** | **YMRS** | ***N*** | **Age** | **Sex (M/F)** | **Field strength (Tesla)** | **Smoothing (mm)** |
| Adler, Levine, DelBello, & Strakowski, 2005 | 32 | 31.2 | 19, 13 | - | - | 8.7 | BD-I | 5 manic, 2 depressed, 25 euthymic | - | - | 27 | 30.5 | 12, 15 | 3 | 12 |
| Almeida et al., 2009 | 27 | **31.9** | 10, 17 | - | 59.3 | 11.1 | BD-I | 17 euthymic, 10 depressed | - | - | 28 | 30.8 | 13, 15 | 3 | 12 |
| Ambrosi et al., 2013 | 20 | 42 | 5, 15 | 35 | 50.0 | 12.6 | BD-II | Euthymic | - | - | 21 | 34.6 | 6, 15 | 1.5 | 8 |
| G. G. Brown et al., 2011 | 15 | 46.2 | 7, 8 | - | 20.0 | 19.1 | BD-I | Depressed | 7.9 | - | 21 | 45 | 10, 11 | 1.5 | 8 |
| S. D. Bruno, Barker, Cercignani, Symms, & Ron, 2004 | 39 | 39.1 | 13, 26 | 59 | 23.1 | 13.2 | 28 BD-I, 11 BD-II | - | - | - | 35 | 34.8 | 10, 25 | 1.5 | 8 |
| X. Chen, Wen, Malhi, Ivanovski, & Sachdev, 2007 | 24 | 38.2 | 6, 18 | 50 | 0.0 | 14.2 | BD-I | - | - | - | 25 | 38.4 | 7, 18 | 1.5 | 12 |
| Z. Chen et al., 2012 | 18 | 32 | 18, 0 | 83 | 16.7 | 4.2 | - | Manic | 3.2 | 24.8 | 27 | 31.3 | 27, 0 | 1.5 | 8 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cui, Li, et al., 2011 | 24 | 28.4 | 15, 9 | - | - | 6.1 | BD-I | Manic | - | 25.9 | 23 | 24.8 | 16, 7 | 3 | 6 |
| de Azevedo-Marques Périco et al., 2011b | 26 | 29.9 | 5, 15 | 23.1 | 42.0 | 0.5 | BD-I | - | 7.5 | 7.4 | 94 | 30.2 | 41, 53 | 2 | 8 |
| Doris, Belton, Ebmeier, Glabus, & Marshall, 2004 | 11 | 40.5 | 6, 5 | - | 45.5 | 16.2 | BD-I | Euthymic | 8.3 | - | 16 | 39.1 | 7, 9 | 3 | 8 |
| Eker et al., 2014 | 28 | 36.4 | 16, 12 | 23 | 17.0 | 16.3 | BD-I | Euthymic | 2.3 | 1 | 30 | 34.7 | 10, 20 | 1.5 | 8 |
| Emsell et al., 2013 | 60 | 42 | 31, 29 | 77 | 56.7 | 13 | BD-I | Euthymic | - | - | 60 | 42 | 31, 29 | 1.5 | 8 |
| Ha, Ha, Kim, & Choi, 2009 | 23 | 35.2 | 8, 15 | 30 | 34.8 | 10.5 | BD-II | 7 depressed, 16 euthymic | 13.1 | - | 23 | 36 | 8,15 | 1.5 | 8 |
| Ha et al., 2009 | 23 | 35.6 | 8,15 | 35 | 43.5 | 10.4 | BD-I | 4 depressed, 19 euthymic | 8.8 | - | 23 | 36 | 8,15 | 1.5 | 5 |
| Haldane, Cunningham, Androutsos, & Frangou, 2008 | 44 | 42.7 | 20, 24 | - | 50.0 | 16.3 | BD-I | Euthymic | 4 | 1.2 | 44 | 43.1 | 20, 24 | 1.5 | 8 |
| Kempton, 2015 | 26 | 42.1 | 9, 17 | 35 | 15.0 | 16.1 | 24 BD-I, 2 BD-II | Euthymic | - | - | 23 | 41.2 | 7, 16 | 3 | 8 |
| Li et al., 2011 | 24 | 28.4 | 15, 9 | 83 | - | 6 | BD-I | 7 depressed, 17 manic | 20 | 25.9 | 36 | 26.6 | 21, 15 | 1.5 | 12 |
| Lochhead, Parsey, | 11 | 38.2 | 6, 5 | - | - | 13.9 | 7 BD-I, 4 BD-II | 11 depressed | 18 | - | 31 | 36 | 16, 15 | 1.5 | 8 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Oquendo, & Mann, 2004 | | | | | | | | | | | | | | | |
| Lyoo et al., 2004 | 39 | 38.3 | 16, 23 | 26 | - | 19.7 | BD-I | 22 depressed, 17 manic | - | - | 43 | 35.7 | 19, 24 | 1.5 | 8 |
| McDonald et al., 2005 | 37 | 40.7 | 15, 22 | 59 | 24.3 | 17.8 | BD-I | - | - | - | 52 | 39.3 | 24, 28 | 1.5 | 8 |
| McIntosh et al., 2004 | 26 | 40.5 | 14, 12 | - | - | - | BD-I | - | - | - | 54 | 35.3 | 23, 26 | 1.5 | 8 |
| McIntosh et al., 2004 | 19 | 39.7 | 7, 12 | - | - | - | BD-I | - | - | - | 54 | 35.3 | 23, 26 | 1.5 | 8 |
| Molina et al., 2011 | 19 | 38.3 | 12, 7 | 84 | 5.3 | 12 | BD-I | Euthymic | - | - | 24 | 34.6 | 16, 8 | 1.5 | 12 |
| Narita et al., 2011 | 17 | 41.4 | 9, 8 | 65 | 11.8 | 6.2 | BD-II | 6 euthymic, 9 depressed, 2 manic | - | - | 84 | 41.1 | 48, 36 | 1.5 | 12 |
| Narita et al., 2011 | 14 | 40.2 | 8, 6 | 76 | 21.4 | 8.6 | BD-II | 2 euthymic, 10 depressed, 2 manic | - | - | 84 | 41.1 | 48, 36 | 3 | 8 |
| Nugent et al., 2006 | 16 | 37 | 5, 11 | 0 | 0.0 | 17 | - | Depressed | - | - | 65 | 38 | 19, 46 | 3 | 8 |
| Nugent et al., 2006 | 20 | 41 | 5, 15 | 31 | 2.8 | 23 | - | Depressed | - | - | 65 | 38 | 19, 46 | 1.5 | 8 |
| Redlich et al., 2014 | 58 | 37.5 | 21, 37 | 26 | 64.0 | 14.2 | BD-I | Depressed | 21 | 3.0 | 58 | 37.7 | 21, 37 | 3 | 8 |
| Rocha-Rego et al., 2013 | 26 | 41.5 | 12, 14 | 38 | 30.8 | 15.8 | BD-I | Euthymic | 6.6 | 1.8 | 26 | 41.3 | 12, 14 | 1.5 | 8 |
| Rocha-Rego et al., 2013 | 14 | 37.6 | 6. 8 | - | 0.0 | 18.8 | BD-I | Euthymic | 4.2 | 1.7 | 14 | 37.4 | 6, 8 | 1.5 | 8 |
| Scherk et al., 2008 | 35 | 43.3 | 18, 17 | 34 | 51.4 | 14.4 | BD-I | Euthymic | 2.5 | 2.6 | 32 | 33.7 | 12, 20 | 1.5 | 8 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Shepherd et al., 2014 | 30 | 39.1 | 12, 18 | - | - | 13.5 | BD-I | - | - | 6.7 | 34 | 32.6 | 16, 18 | 3 | 8 |
| Stanfield et al., 2009 | 66 | 36.4 | 30, 36 | - | 47.0 | 15.4 | BD-I | Euthymic | - | - | 66 | 39 | 31, 35 | 1.5 | 12 |
| Tang et al., 2014 | 27 | 32 | 10, 17 | 33 | - | 4.2 | - | Depressed | 19.7 | 1 | 27 | 32.6 | 11, 16 | 3 | 8 |
| Yatham et al., 2007 | 15 | 36 | 6, 9 | - | 0.0 | 3.9 | BD-I | Manic | - | 27 | 15 | 36 | 6, 9 | 1.5 | 8 |
| Yüksel et al., 2012 | 27 | 32.9 | 17, 10 | 48 | 0.0 | - | BD-I | 18 manic, 5 mixed, 4 euthymic | 7.2 | 22.8 | 43 | 36.4 | - | 3 | 12 |

**Table 4-5. Characteristics of bipolar disorder studies included in the meta-analysis. M = male, F = female, y = years, HAMD-17 = Hamilton Depression Rating Scale 17-item, BD-I = bipolar disorder type I, BD-II = bipolar disorder type II, YMRS = Young Mania Rating Scale**

| Peak MNI coordinate | *Z* | P | Voxels | Brodmann areas | Regions |
|---|---|---|---|---|---|
| **Major Depression < Healthy Controls** | | | | | |
| -66,-16,-12 | 2.64 | 0.002 | 19 | 21 | Left middle temporal gyrus |
| -30,-72,44 | 2.51 | 0.003 | 18 | 7 | Left inferior parietal lobule |
| -36,-34,-18 | 2.74 | 0.001 | 13 | 37 | Left fusiform gyrus |
| -4,-44,-22 | 2.46 | 0.004 | 13 | - | Cerebellar vermis |
| **Major Depression > Healthy Controls** | | | | | |
| -10,-72,0 | -1.04 | <0.001 | 207 | 18 | Left lingual gyrus |
| -8,-52,18 | -1.06 | <0.001 | 197 | 30 | Left precuneus |
| -48,-50,-40 | -1.01 | <0.001 | 129 | - | Left cerebellum, crus I |

**Table 4-6. Clusters showing differences between major depression and controls that did not meet our criteria for robustness**

| Peak MNI coordinate | *Z* | P | Voxels | Brodmann areas | Regions |
|---|---|---|---|---|---|
| -46,4,4 | 1.82 | <0.001 | 436 | 48 | Left insula |
| 2,34,-16 | 1.33 | <0.001 | 248 | 11 | Left gyrus rectus, medial orbitofrontal cortex |
| 4,-2,42 | 1.15 | <0.001 | 203 | 23, 24 | Right midcingulate area |
| 22,2,-18 | 1.33 | <0.001 | 207 | 34 | Right amygdala |
| 52,6,-20 | 1.23 | <0.001 | 173 | 21 | Right temporal pole, middle temporal gyrus |
| -22,-16,-14 | 1.50 | <0.001 | 51 | 35 | Left hippocampus |
| -26,20,60 | 1.18 | <0.001 | 42 | 8 | Left middle frontal gyrus |

**Table 4-7. Clusters showing significant between study heterogeneity in major depression**

| Peak MNI coordinate | *Z* | P | Voxels | Brodmann areas | Regions |
|---|---|---|---|---|---|
| **Bipolar Disorder < Healthy Controls** | | | | | |
| -62,-60,-10 | 2.71 | 0.002 | 20 | 37 | Left inferior temporal gyrus |
| 36,60,6 | 2.64 | 0.002 | 13 | 10 | Right middle frontal gyrus |
| **Bipolar Disorder > Healthy Controls** | | | | | |
| -14,-60,-44 | -1.21 | 0.003 | 23 | - | Left cerebellum, hemispheric lobule VIII |
| 4,-14,-22 | -1.33 | 0.002 | 16 | - | Right pons |
| -14,-30,-34 | -1.39 | 0.001 | 19 | - | Middle cerebellar peduncles |
| 4,-38,-18 | -1.17 | 0.003 | 20 | - | Cerebellar vermis |
| 42,-56,6 | -1.34 | 0.002 | 20 | 37 | Right middle temporal gyrus |
| -10,46,-30 | -1.38 | 0.001 | 11 | 11 | Left orbitofrontal cortex |
| -32,-54,38 | -1.22 | 0.003 | 11 | 40 | Left inferior parietal gyrus |

**Table 4-8. Clusters showing differences between bipolar disorder and controls did not meet our criteria for robustness**

| Peak MNI coordinate | *Z* | P | Voxels | Brodmann areas | Regions |
|---|---|---|---|---|---|
| 8, 12, 12 | 5.88 | <0.001 | 657 | 25 | Right caudate nucleus |
| -46,38,-14 | 4.42 | <0.001 | 425 | 47 | Left inferior frontal gyrus |
| 30,-36,-18 | 3.297 | 0.001 | 169 | 37 | Right fusiform gyrus |
| 48,36,-12 | 3.94 | <0.001 | 119 | 47 | Right inferior frontal gyrus |
| -58,-66,-12 | 3.33 | <0.001 | 61 | 37 | Left inferior occipital gyrus |
| 6,18,22 | 2.82 | 0.002 | 55 | 24 | Right anterior cingulate cortex |
| 50,16,2 | 2.77 | 0.002 | 33 | 45, 48 | Right inferior frontal gyrus |
| 62,-20,-4 | 2.72 | 0.003 | 30 | 21, 22 | Right superior temporal gyrus, middle temporal gyrus |
| 6,-14,10 | 3.03 | 0.002 | 30 | - | Right thalamus |
| -20, -22, -22 | 2.89 | 0.002 | 28 | 30 | Left parahippocampal gyrus |

| | | | | | |
|---|---|---|---|---|---|
| -42, -46, 46 | 2.60 | 0.003 | 24 | 40 | Left inferior parietal gyrus |
| -52, 34, 24 | 3.39 | 0.001 | 18 | 45 | Left inferior frontal gyrus, pars triangularis |

**Table 4-9. Clusters showing significant between study heterogeneity in bipolar disorder**

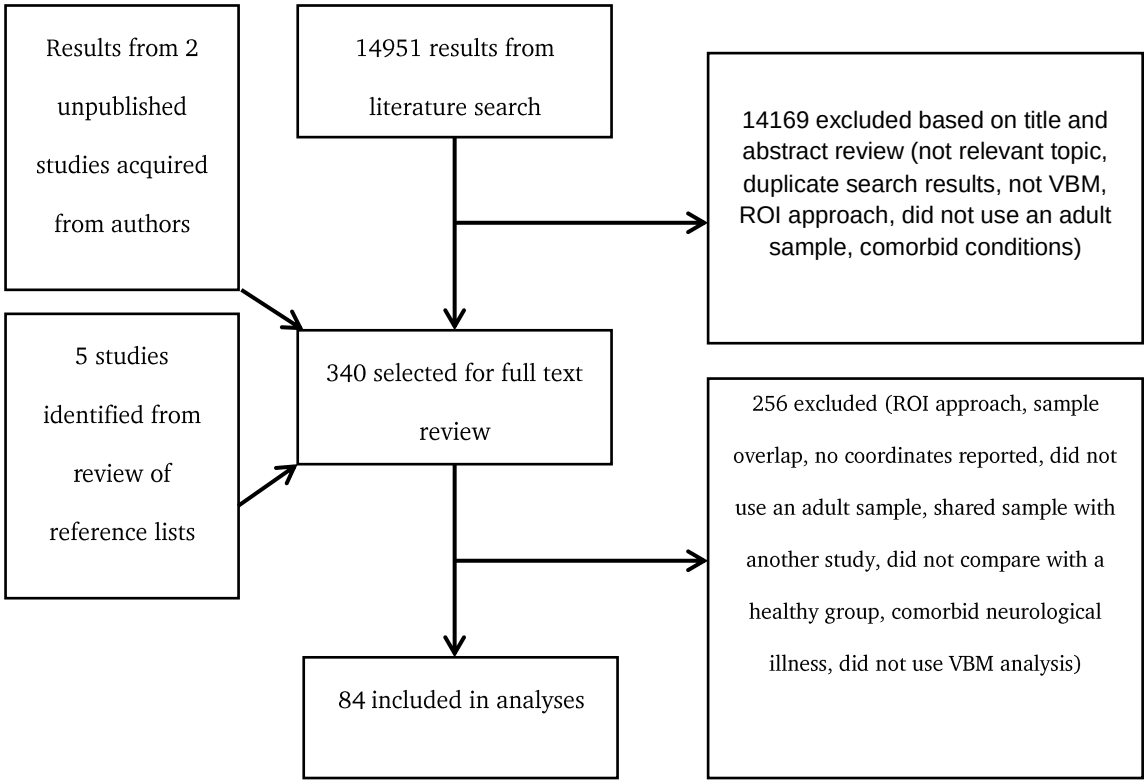


**Figure 4-4. Literature search results**

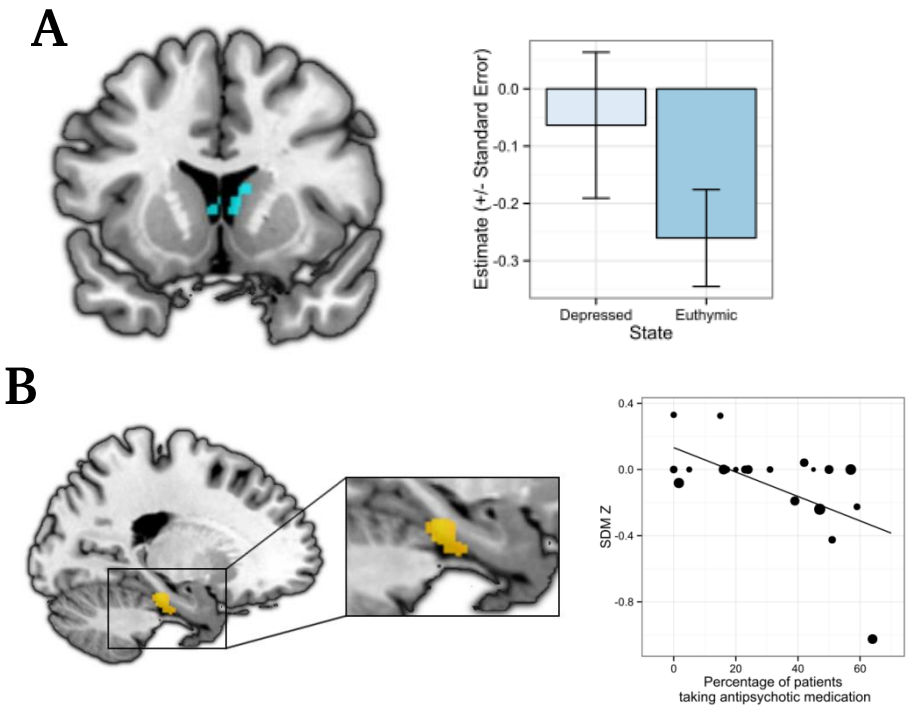


**Figure 4-5. A) Results of mood state comparison in bipolar disorder. B) Results of meta-regression with antipsychotic medication load in bipolar disorder.**

# 5 Glutamatergic Hypofunction in Medication-Free Major Depression: Secondary Effects of Affective Diagnosis and Relationship To Peripheral Glutaminase

## 5.1 Introduction

Major depression and bipolar disorder are common conditions with substantial negative consequences for sufferers (Kessler et al., 2003; Merikangas et al., 2007). Understanding the biological changes associated with these conditions is a major research priority, and a better understanding of their biological basis could lead to improved diagnosis and treatment.

Over the last two decades, neuroimaging has brought a deeper understanding of neurobiological alterations associated with these conditions, and researchers are moving towards developing these methods to diagnose and treat affective disorders (Wise et al., 2014). In particular there is now a substantial literature detailing neurochemical abnormalities in both major depression and bipolar disorder (Arnone, Mumuni, Jauhar, & Cavanagh, 2015; Shrestha et al., 2012; M. J. Taylor, 2014a), and in recent years research into glutamatergic neurotransmission specifically has been pursued with increasing interest spurred by studies demonstrating that ketamine, an NMDA receptor antagonist, can rapidly treat both unipolar and bipolar depression (McGirr et al., 2015). This research has been aided by developments in magnetic resonance spectroscopy (MRS), a method that allows simple, non-invasive measurement of local glutamate and glutamine levels *in vivo*.

Despite this, findings at present are inconsistent, and there are particularly divergent results from studies in major depression and bipolar disorder (M. J. Taylor, 2014a).

Glutamate and glutamine levels are typically found to be reduced in unipolar depression, most notably in prefrontal regions such as the anterior cingulate cortex (Arnone et al., 2015), while studies in bipolar disorder suggest an increase in glutamate in this region (M. J. Taylor, 2014a). These results are difficult to reconcile with the apparent efficacy of ketamine in treating both unipolar and bipolar depression. In particular, given the tendency of ketamine to increase glutamate levels (Stone et al., 2012), it is unclear why such a manipulation would improve depressive symptoms in bipolar disorder if it is indeed associated with increased glutamatergic neurotransmission. One possible explanation for these contradictory results is that studies examining glutamate levels in these disorders have typically used voxels placed in the perigenual anterior cingulate cortex, an area in which glutamate levels appear to be unaffected by ketamine administration (M. J. Taylor, Tiangga, Ní Mhuircheartaigh, & Cowen, 2012). Ketamine however appears to have marked effects in a more dorsal region of the anterior cingulate cortex (Stone et al., 2012) and it is possible that it is in this region that it exerts antidepressant effects.

Additionally, while MRS provides an accurate way to measure brain glutamate concentration in vivo, the identification of an easily measurable peripheral marker of glutamatergic function capable of indicating an affective state would simplify the potential use of glutamate as a diagnostic marker in the clinic. One marker of particular interest is glutaminase, an enzyme that catalyses the conversion of glutamine to glutamate. Genetic variation in the GLS1 gene, which codes for glutaminase, is associated with levels of central glutamate and glutamine as measured using MRS (Öngür et al., 2011), indicating that this may be a marker of brain glutamate levels.

Here we measured glutamate levels in a group of individuals with unipolar and bipolar major depression in the same voxel location where ketamine has been shown to affect glutamate levels (Stone et al., 2012). We predicted a reduction in glutamate levels associated with depressive state irrespective of affective diagnosis. Additionally, we measured peripheral glutaminase in serum and investigated changes in relation to brain glutamate. We hypothesised that peripheral glutaminase levels would positively correlate with anterior cingulate cortex glutamate levels. Importantly, we used a sample of medication-free patients to ensure that results were not influenced by current pharmacotherapy.

## 5.2 Methods

### *5.2.1 Participants*

Participants were recruited through public advertisements and from local psychological therapy services (Wise, Arnone, Marwood, et al., 2016a). Patients met DSM-IV criteria for a current major depressive episode in the context of unipolar or bipolar disorders determined by a clinical interview with a psychiatrist based on the Mini International Neuropsychiatric Interview (MINI, Sheehan et al., 1998). Patients with any other DSM-IV axis I/II diagnoses were excluded. Healthy volunteers did not meet criteria for any current or past psychiatric diagnoses, as assessed by the MINI, and reported no family psychiatric history in first-degree relatives. Patients were enrolled if they experienced 1) moderate to severe depressive symptoms (score of ≥18) established with the clinician-rated Montgomery-Åsberg Depression Rating Scale (MÅDRS; Montgomery & Åsberg, 1979); 2) were psychotropic medication-free for ≥2 weeks (≥4 weeks for fluoxetine) and were not receiving any psychological

intervention; and 3) did not experience current clinically significant symptoms of elation established by using the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978). Diagnoses of bipolar disorder were retrospective and supplemented by review of medical notes and collateral information where necessary. Historic hypomanic symptoms were assessed using the Hypomania Checklist 33-item (Angst et al., 2005; Feng et al., 2016, p. 33). All participants were excluded if they reported any illicit substance use in the previous two months, had any physical health conditions or received pharmacotherapy that could affect safety, or interfere with data acquisition, analyses or interpretation. All participants were screened for MRI safety. The research was approved by the relevant local ethics committee and informed consent was obtained from each participant. Participants received a small financial compensation for taking part in the research.

### *5.2.2 Magnetic resonance spectroscopy*

1H-Magnetic resonance spectroscopy data were acquired using a GE MR-750 3T system with a 12-channel head coil. A water supressed PRESS sequence was used (TR=3s, TE=30ms). As in previous work (Stone et al., 2012), a 20 x 20 x 20mm voxel was placed 16mm above the most anterior portion of the corpus callosum, on the midline, adjusted manually to ensure optimal coverage of grey matter. This resulted in coverage of the dorsal portion of Brodmann areas 24 and 32 (Figure 5-1). T1-weighted structural images were also collected to provide measures of intracranial volume (Echo time = 3.02ms, repetition time = 7.31ms, inversion time = 400ms, flip angle = 11°, 270mm x 270mm field of view, 196 slices. slice thickness = 1.2mm)(Jack et al., 2010).

**Figure 5-1. Illustration of anterior cingulate cortex MRS voxel location on a typical participant**

Analysis of the MRS spectra was conducted using LCModel version 6.3 (Provencher, 2001), and spectra were visually inspected to ensure that the LCModel fit was acceptable. Glutamate concentrations were normalised to creatine to account for individual differences in the absolute volumes of metabolites.

### *5.2.3 Glutaminase measurement*

To measure glutaminase levels in serum samples a commercial Enzyme-linked Immunosorbent Assay Kit for Glutaminase (Cloud-Clone Corp, Buckingham,UK) was used according to the manufacturer's instructions. The protein glutaminase standard was diluted in standard diluent to generate a standard curve with seven points, ranging from 0.312 to 20 ng/ml. Subsequently, 100 µl of prepared standards and samples (serum dilution 1:10) was added to the wells of the immunoassay plate pre-coated with a specific antibody against glutaminase and incubated at 37 °C for 2 h. The primary and secondary antibodies (1:100 dilution) were added to the wells and incubated at 37 °C for 1 h and 30 min respectively. Subsequently, 100 µl of 3,3′,5,5′-

tetramethylbenzidine substrate (TMB) were added to each well and incubated for 15 min in the dark. Finally, 100 µl of Stop Solution was added and absorbance was measured at 450 nm with a microplate photometric reader (DV990BV4, GDV, Milan, Italy). Sample concentration was calculated by interpolating the sample measurement in the standard curve. The sensitivity of the human glutaminase ELISA kit was determined to be 0.312 ng/ml. Human glutaminase ELISA kit is specific for glutaminase and has been certified for the detection of human glutaminase. Blood samples were unable to be collected from one subject in the unipolar depression group and this subject was excluded from analyses involving glutaminase levels.

*Intracranial volume*

We compared intracranial volumes between groups to ensure that any group differences were not reflective of global alterations in brain volume. Intracranial volume was calculated by segmenting T1-weighted structural images from each subject using FreeSurfer (www.freesurfer.net).

### *5.2.4 Statistical analysis*

All statistical analyses were performed using R (www.r-project.org). To assess whether depressed patients differed from controls we compared glutamate levels between both depressed groups combined and controls using an independent measures *t*-test, adjusted for age and sex. To test whether there were any differences between unipolar and bipolar depression, we compared the patient groups against one another using an independent measures t-test. To further explore diagnostic differences in central glutamate levels we used a one-way ANCOVA with age and sex as covariates. Significant effects were further explored using t-tests, corrected for multiple comparisons with the Benjamini-Hochberg method (Benjamini & Hochberg, 1995).

Correlations between glutamate levels and clinical variables and peripheral markers were analysed using partial Pearson correlations, correcting for age and sex.

## 5.3 Results

### *5.3.1 Participants*

Twenty patients with unipolar depression, nine with bipolar depression (seven bipolar disorder type II, and two with type I) and 20 healthy controls, matched on age and handedness took part in the study. Patients with unipolar depression and healthy controls were matched on sex, however the bipolar group had a higher proportion of males than the other groups ($X^2 = 4.49$, $p = 0.034$). The two depressed groups were comparable on clinical variables including depression severity, current manic symptoms and illness duration, but the bipolar group had experienced significantly more depressive episodes ($W = 34.5$, $p = 0.007$, non-parametric test used to non-normally distributed data). Demographic and clinical details for the combined depressed group, as used in further analyses, are described in Table 5-1.

| | Depression | Healthy control | *p* |
|---|---|---|---|
| **Age in years** | 30.14 (7.04) | 30.05 (6.71) | 0.97 |
| **Sex: male, female** | 6, 23 | 2, 18 | 0.32 |
| **MÅDRS** | 26.59 (4.59) | 0.95 (1.39) | < .001 |
| **YMRS** | 2.21 (1.82) | 0.1 (0.31) | < .001 |
| **Duration of illness in years** | 7.65 (6.40) | - | - |
| **Number of depressive episodes** | 5.66 (11.94) | - | - |
| **Total intracranial volume** | 1425.89 (144.90) | 1447.76 (113.11) | 0.56 |

**Table 5-1. Demographic and clinical information for all participants. Values are reported as mean (SD), except the number of episodes which is reported as median (SD) due to skewed data. MÅDRS: Montgomery-Åsberg Depression Rating Scale, YMRS: Young Mania Rating Scale.**

### *5.3.2 Magnetic resonance spectroscopy*

The combined unipolar and bipolar depressed group had significantly lower glutamate levels in the anterior cingulate cortex than healthy volunteers ($t(46.62) = -2.82$, $p = 0.014$, $d = -0.79$). To test our hypothesis that this was not an effect of diagnosis, we compared unipolar vs. bipolar groups and found no significant difference in glutamate levels ($t(12.63) = -0.07.$, $p = 1$, $d = -0.03$). Total intracranial volume did not differ between controls and the depressed group ($t(41.60) = -1.71$, $p = 0.20$) or between unipolar and bipolar depression ($t(18) = 0.23$, $p = 1$, suggesting that this was not related to global brain volume.

We performed further exploratory analyses to investigate potential effects of diagnosis. A one-way ANCOVA revealed a main effect of diagnosis on glutamate levels ($F(2, 46) = 3.72$, $p = 0.032$, $\eta^2 = 0.14$, Figure 5-2). Post-hoc tests showed that the unipolar group had significantly reduced glutamate levels relative to controls ($t(38) = -2.63$, $p = 0.03$, $d = -0.90$). The bipolar group had reduced levels of glutamate relative to

controls, however this was not statistically significant ($t(27) = -1.75$, $p = 0.14$, $d = -0.70$).

There was no significant correlation between glutamate levels and depression severity, as measured by the MÅDRS, in the combined depressed group ($R_{partial}(25) = 0.034$, $p = 0.87$). There was also no correlation between glutamate levels and self-reported hypomanic symptoms measured using the hypomania checklist ($R_{partial}(23) = 0.011$, $p = 0.62$).

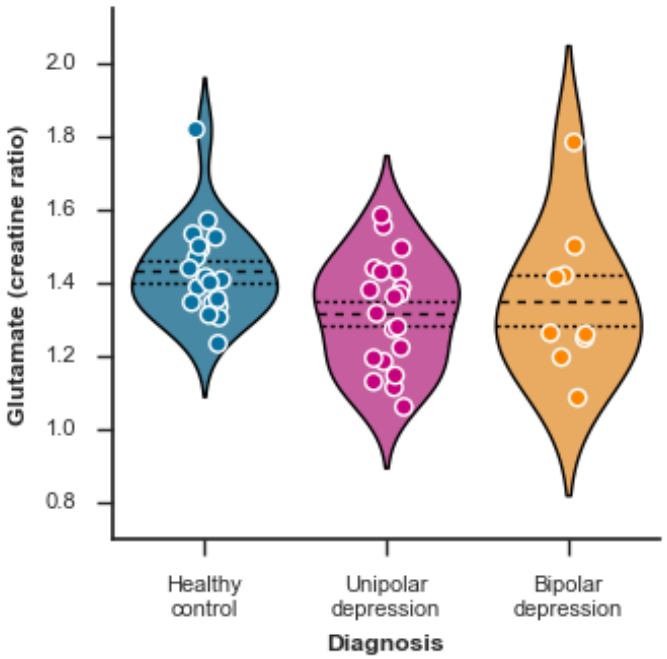


**Figure 5-2. Glutamate levels in anterior cingulate cortex of healthy controls, people with unipolar depression, and bipolar depression. Coloured areas represent a histogram of the data in each conditions, while circles represent the individual data point.**

### *5.3.3 Relationship between glutamate function and peripheral glutaminase*

There were no differences in glutaminase levels between the combined unipolar and bipolar depressed groups and controls ($t(28.3) = -1.21$, $p = 0.48$, $d = -0.39$) or between unipolar and bipolar disorders ($t(13.76) = -0.96$, $p = 0.72$, $d = -0.40$).

Analysis of the relationship between prefrontal glutamate levels and peripheral glutaminase indicated a positive but non-significant correlation between these measures ($R_{partial}(48) = 0.25$, $p = 0.09$, Figure 5-3).

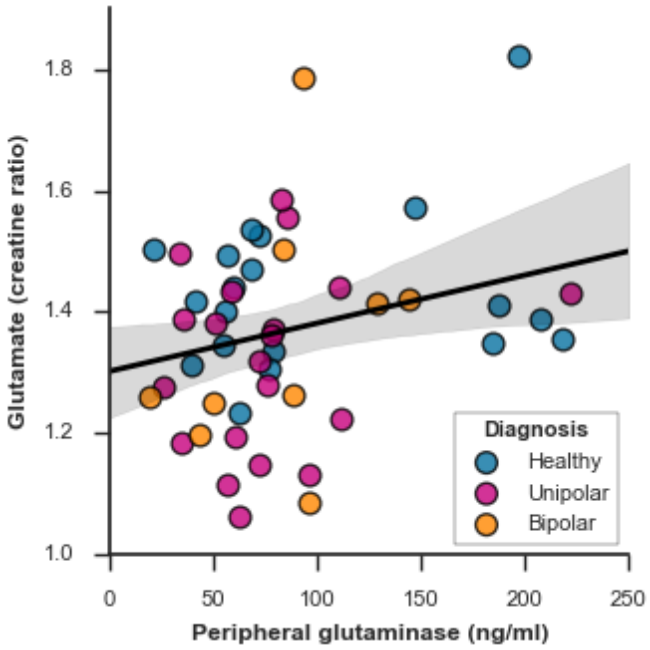


**Figure 5-3. Relationship between peripheral glutaminase levels and anterior cingulate glutamate measured using MRS**

## 5.4 Discussion

We measured dorsal anterior cingulate cortex glutamate levels in unmedicated unipolar and bipolar major depression and found that glutamate was reduced relative to controls in the depressive state irrespective of diagnosis, although this effect only reached significance in the unipolar group. Additionally, our results suggest that alternatives to peripheral glutaminase levels may be preferable to index central glutamate levels.

Our finding of reduced glutamate in unipolar depression is in line with previous research indicating glutamatergic hypofunction in unipolar depression (Arnone, Mumuni, Jauhar, & Cavanagh, 2015). In bipolar disorder the majority of studies tend to indicate an increase in glutamate levels in the prefrontal cortex (M. J. Taylor,

2014a), which contrasts with our finding of a reduction in glutamate levels. Although this reduction was not statistically significant, given the challenges associated with recruiting medication-free individuals with bipolar depression and the resulting issues with statistical power, it is important to consider these results in the context of previous research in similar patients. The only other study to date to investigate anterior cingulate cortex glutamate levels in medication-free patients with currently experiencing a depressive episode in the context of bipolar disorder also reported a non-significant reduction in glutamate in the anterior cingulate cortex (J. Xu et al., 2013) and our results, taken together with this previous work, suggest that bipolar depression in the absence of medication may be associated with glutamatergic hypofunction in the anterior cingulate cortex. A reduction in glutamate levels as expression of state rather than diagnosis concords with the reported clinical efficacy of ketamine in both unipolar and bipolar depression, known to increase glutamatergic neurotransmission in the brain region investigated in this study (Stone et al., 2012). In addition to medication status and mood state, topographical differences in prefrontal voxel placement might explain discrepancies between our findings and the literature. Most studies have used voxels placed in the perigenual anterior cingulate cortex, an area less affected by ketamine administration (M. J. Taylor et al., 2012).

The absence of a significant difference in peripheral glutaminase levels in subjects with unipolar and bipolar depression vs. healthy controls suggests that variations in this enzyme are unlikely to reflect differences in central glutamate levels. The lack of significant correlations between peripheral glutaminase levels and indexes of glutamatergic function measured in this study suggests that peripheral glutaminase does not accurately reflect glutamatergic neurotransmission in the anterior cingulate cortex. This is in agreement with preliminary studies in healthy individuals that measured glutamatergic function with MRS in a different location within the medial

prefrontal cortex (Shulman et al., 2006) and suggests that alternative peripheral markers that may better reflect glutamatergic function at brain level should be identified.

The most important implication of this work is that it provides a putative explanation for the effectiveness of fast acting glutamatergic agents such as ketamine, known to increase cortical glutamate release, in treating major depressive episodes (Rowland et al., 2005; Stone et al., 2012). Ketamine has been shown to be effective in both unipolar and bipolar major depression (McGirr et al., 2015), and these results have been difficult to fully understand in the context of previous research showing increased glutamate levels in bipolar disorder (M. J. Taylor, 2014a). We propose that the region within the prefrontal cortex centred around Brodmann area 32 might be key to understanding glutamatergic function in affective disorders. Notably, this region has been causally implicated in the processing of negative affect (Tolomeo et al., 2016), and the presence of glutamatergic hypofunction in this area may contribute to disturbances in affective regulation. This phenomenon is likely to be mediated by an increased baseline GABAergic interneuron tone, known to modulate glutamatergic hypofunction (Stone et al., 2012). In this context, ketamine may act by inhibiting GABAergic interneurons, resulting in increased glutamatergic release as demonstrated in healthy controls (Stone et al., 2012).

It is also possible that decreased levels of glutamate in this region is a reflection of grey matter volume reduction, which we have recently demonstrated in both unipolar and bipolar depression (Arnone et al., 2016; Wise, Radua, Via, et al., 2016). This seems unlikely however, as we used ratios of glutamine to creatine so that our results should not be a direct effect of reduced grey matter volume. Another factor to consider is that a reduction in the integrity of the white matter callosal pathways connecting

the two hemispheres in affective disorders might also glutamatergic function (Wise, Radua, Nortje, et al., 2016). This would be in agreement with recent theories suggesting that the metabolic interplay between glutamatergic neurons and astrocytes in the synapse might be central to understanding abnormalities in this neurotransmitter in affective disorders and could potentially contribute to the therapeutic effects of fast acting antidepressants (Arnone, Mumuni, Jauhar, Condon, et al., 2015).

Our findings indicate that the dorsal anterior cingulate cortex appears to be central to understanding the role of glutamatergic neurotransmission in affective disorders. Further investigations dissecting the functional neuroanatomy of this region are warranted, particularly in relation to the role played by GABAergic interneurons. Parvalbumin expressing GABAergic interneurons projecting from the medio-dorsal thalamic nucleus to the prefrontal cortex appear crucially important to investigate in future studies as they play a critical role in modulating the functional flexibility of the dorsal part of the anterior cingulate cortex when integrating sensory information (Delevich, Tucciarone, Huang, & Li, 2015), and are regulated by glutamatergic neurotransmission (Homayoun & Moghaddam, 2007). Newly developed methods of spatially mapping glutamate may prove valuable in this respect (e.g. Cai et al., 2013).

Strengths of this study include the exclusion of the effects of pharmacological or psychological therapies on the data. Although we cannot entirely exclude effects of previous treatments, we can be confident that our results are not an effect of current treatment. Additionally, the majority of our patients in the unipolar group were experiencing their first depressive episode and results are unlikely to represent “scar” effects. Diagnoses were also thoroughly examined for all patients to ensure that cases were not inappropriately classified.

Limitations include the small number of bipolar participants due to the difficulty of recruiting unmedicated, currently depressed, patients with this condition. Hence it is important to consider our findings in the context of previous research demonstrating a similar effect in unmedicated bipolar depression (J. Xu et al., 2013). The community sample we included in the research reflects a lower severity index than an inpatient sample or more complex forms of illness with comorbidities, which we excluded. Also the bipolar sample most entirely comprised patients with bipolar type II, hence it is not possible to generalise findings to bipolar type I. For this reason we cannot entirely exclude the possibility that more severe cases and/or psychotic presentations may differ in relation to glutamatergic function, perhaps similarly to glutamatergic and morphometric alterations observed in schizophrenia (Arnone et al., 2009; Merritt, Egerton, Kempton, Taylor, & McGuire, 2016). It is also not possible to comment on specific state effects as we did not include groups of patients experiencing euthymia or elated mood. Lastly, by the very nature of the selected voxel of interest and the hypotheses tested in this study it is not possible to comment on glutamatergic function in other brain regions.

Future research is warranted to examine brain glutamate function in different mood states, and the modulatory effect of treatment interventions and clinical improvement, preferably with a longitudinal approach. Future studies would benefit from recruiting larger samples of patients with bipolar disorder in order to properly test effects of mood state and diagnosis, in particular with regard to bipolar subtypes. However given the substantial challenges associated with recruiting medication-free individuals with bipolar disorder experiencing a depressive episode, this will likely require large-scale multicentre studies to maximise recruitment. Additionally, research using functional MRS acquisition (Apšvalka, Gadie, Clemence, & Mullins, 2015) during emotion

processing tasks or mood induction may prove useful to further evaluate state effects and elucidate the mechanisms linking glutamatergic function to mood.

In summary, we investigated glutamate levels in the dorsal anterior cingulate cortex in unmedicated subjects with bipolar and unipolar depression and demonstrated glutamatergic hypofunction in unipolar depression, with a trend towards a significant reduction in bipolar depression. Evaluation of circulating glutaminase indicated the need to identify an alternative proxy for central brain glutamate if accessible biomarkers for disease-related alterations in central glutamate are to be developed.

# 6 An Investigation into Morphometric Correlates of Bipolarity in Unmedicated Major Depression

## 6.1 Introduction

Affective disorders such as major depression and bipolar disorder are common conditions with profound effects on sufferers and society (Kessler et al., 2003; Merikangas et al., 2007). There is mounting clinical evidence supporting the existence of a bipolar spectrum within depressive disorders (Akiskal et al., 2000; Angst, 2007; Cassano et al., 2004), with individuals high in hypomanic symptoms being more likely to develop a severe illness trajectory (Woo et al., 2015) and to attempt suicide (Cassano et al., 2004). An identifiable biological signature of bipolarity is a research priority to improve diagnostic precision and help develop tailored treatments that could be used at the earliest opportunity (Wise et al., 2014).

At brain level research to date has indicated a degree of overlap in grey matter loss between unipolar and bipolar disorders in the medial prefrontal cortex and insula bilaterally (Arnone et al., 2016; Kempton et al., 2011; Selvaraj et al., 2012; Wise, Radua, Nortje, et al., 2016; Wise, Radua, Via, et al., 2016). It is also known that specific grey matter loss tends to occur selectively in unipolar major depression compared to bipolar disorder in the left hippocampus, right middle temporal gyrus, and right dorsolateral prefrontal cortex, (Wise, Radua, Via, et al., 2016). However to date no studies have explored structural correlates of correlates of bipolarity as a spectrum, despite growing clinical and epidemiological evidence that bipolarity is better characterised as a dimensional construct than a dichotomous diagnosis (Angst, 2007). Two studies to date have researched functional brain level correlates of the bipolar spectrum as a dimensional construct. Fournier and others (2013)

demonstrated that right amygdala responses to positive emotions were stronger in individuals with unipolar depression reporting greater levels of manic symptoms, while Yang *et al* (2016) reported alterations in resting state activity in those with unipolar depression who reported high levels of hypomanic symptoms. Together these findings indicate that a bipolar diathesis within unipolar depression is associated with altered function in neural systems underlying affective processing, and highlight the need for similar studies of brain structure.

In this study, we focused on identifying a structural biological signature of bipolarity within a sample of medication-free individuals experiencing a major depressive episode. We aimed to identify specific patterns of grey matter volume alteration predicting self-reported measures of bipolarity. A multivariate approach, using machine-learning methods, was chosen in view of two distinct advantages over traditional univariate methods for analyses of this type. Firstly, their multivariate nature allows detection of complex patterns represented across multiple voxels, unlike traditional univariate analyses where each voxel is analysed independently. Secondly, this method allows prediction of bipolarity scores at the individual level, an important step if any identified signature of bipolarity were to have translational value. We also performed traditional univariate analyses for comparison with more traditional neuroimaging methods.

Importantly, we included a clinical sample that reported a wide range of self-reported hypomanic/manic symptoms, including those diagnosed with both unipolar and bipolar depression, to represent the full spectrum of bipolar symptoms from subclinical through to clinically significant manic episodes. Critically, our aim was not to differentiate unipolar from bipolar diagnoses, a subject that previous studies have addressed in detail (Redlich et al., 2014), but instead to identify a structural basis for

bipolarity as a dimensional construct. Guided by regions showing significant differences in grey matter volume between unipolar and bipolar disorders in our previous meta-analysis (Wise, Radua, Via, et al., 2016), we expected that variation in grey matter volume in the right dorsolateral prefrontal cortex, right inferior temporal gyrus, and left hippocampus would predict self-reported bipolarity.

## 6.2 Methods

### *6.2.1 Participants*

Participants were recruited from public advertisements (Wise, Arnone, Marwood, et al., 2016b) and local psychological therapy services. All participants were assessed for Axis I diagnoses by a psychiatrist and a trained researcher using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Diagnoses of bipolar disorder were confirmed based on review of medical notes and collateral information where necessary. Depressive symptom ratings between raters were evaluated on an independent set of patients, and inter-rater reliability was found to be high (Intraclass correlation coefficient = 0.96, $p$ = .004).

Patients met Axis I DSM-IV criteria for unipolar major depression or bipolar disorder, as judged through a clinical interview based on the MINI (Sheehan et al., 1998) and were: 1) experiencing a moderate to severe depressive episode at the time of inclusion assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS, Montgomery & Asberg, 1979) with a score of ≥18; 2) medication-free for ≥2 weeks (≥4 weeks for fluoxetine) and not receiving any psychological intervention at the time of scanning; and 3) were right handed (assessed using the Edinburgh Handedness Scale (Oldfield, 1971). A bipolar disorder diagnosis was further substantiated by

review of medical notes and collateral information whenever possible and the Young Mania Rating Scale (Young et al., 1978) was used to exclude current hypomania/mania in these patients. Duration of illness was calculated as the number of years since the onset of any mood episode.

Matched healthy controls were screened in an interview based on the MINI, and had no current or past psychiatric diagnoses, and no history of psychiatric illness in first-degree relatives. Participants were excluded if they reported any illicit substance use in the previous two months, had any unstable medical condition or took any medication that could affect safety or study results, analyses or interpretation. All participants were screened for MRI safety.

Historical hypomanic symptoms were assessed using the 33-item hypomania checklist (HCL), a self-report measure that has been shown to reliably detect symptoms of hypomania (Angst et al., 2005; Feng et al., 2016). The questionnaire features a range of symptoms present during "high" states (e.g. "I talk more", "I need less sleep") and the overall score is calculated as total number of items that the subject endorses. This questionnaire was chosen as it is sensitive to variation in hypomanic symptoms and provides a continuous measure of bipolarity, rather than a categorical diagnosis. This total score was used for further analysis in this study.

The research was approved by the relevant local ethics committee and informed consent was obtained from each participant. All participants were compensated for taking part in the research.

### 6.2.2 *Structural imaging*

High resolution T1-weighted structural images were acquired on one of two identical GE MR750 3 Tesla scanners at the same site, using identical sequences (TR=7.31ms, TE=3.02ms, 256 x 256 matrix, 196 slices, voxel size = 1.2 x 1.05 x 1.05mm).

### 6.2.3 *Voxel-based morphometry*

Structural images were pre-processed using voxel-based morphometry in SPM12 *(www.fil.ion.ucl.ac.uk/spm)*. Images were segmented into grey matter, white matter, and cerebrospinal fluid and processed with DARTEL (Ashburner, 2007) before being normalised to MNI space. The modulated grey matter images were then smoothed with an 8mm FWHM Gaussian kernel and the resulting images were used as input for further analyses.

### 6.2.4 *Machine learning*

To identify distributed patterns of grey matter volume alteration that predict bipolarity, we used support vector regression (Smola & Vapnik, 1997) with a linear kernel implemented in the Scikit-learn module for Python (Pedregosa et al., 2011). This is an extension of the support vector machine classification method that aims to predict a continuous target variable, in our case HCL scores, by finding a linear hyperplane with minimal distance from the observed data points, subject to penalisation of residuals greater than $\varepsilon$ by constant $C$ to limit overfitting. This can be used to predict target values associated with previously unseen data. Predictive accuracy was assessed using leave-one-out cross validation. This involves training the model on all but one of the observations and testing its predictive accuracy on the withheld sample, repeating this process for every possible combination of training and testing data. We assessed the statistical significance of the results using permutation

testing with 1000 permutations, whereby the model was repeatedly evaluated on data with target HCL scores randomly reshuffled to provide an empirically derived null distribution which is used to determine the probability of the observed predictive accuracy occurring under the null hypothesis. The value of parameters *C* and ε were set using random search (Bergstra & Bengio, 2012). Prediction accuracy was quantified using mean-squared error (MSE), however we also report mean absolute error for ease of interpretation.

We also examined whether it was possible to predict hypomanic symptoms in healthy controls. For this analysis, both training and testing were conducted in the healthy control group, using leave one out cross-validation as was used in the patient group.

Reducing the dimensionality of input data, a process known as feature selection, is crucial to ensure accurate predictions when using machine learning methods (Mwangi, Tian, & Soares, 2013). We focused on brain regions shown to differentiate unipolar from bipolar disorder in our previous meta-analysis (Wise, Radua, Via, et al., 2016) and created a region of interest mask which included left hippocampus, right middle temporal gyrus, right middle frontal gyrus, cerebellar vermis, and left inferior parietal lobule (Wise, Radua, Via, et al., 2016). Thus feature selection was based on independent data and does not result in "double dipping" (Mwangi et al., 2013). Feature weights from the support vector regression were extracted and plotted to identify the voxels contributing most highly to the prediction.

### *6.2.5 Univariate analyses*

To compare the performance of the support vector regression model in detecting regions of grey matter variation predicting bipolarity against traditional univariate methods, linear regression analyses in SPM were used to identify regions of grey

matter alteration that correlated with HCL scores, covarying for intracranial volume and scanner. As with the support vector regression, statistical analyses used a region of interest approach, focusing on regions identified in our previous meta-analysis (Wise, Radua, Via, et al., 2016). Statistical maps were thresholded with a voxelwise threshold of < .001 uncorrected and a cluster-wise significance threshold of < .05 FDR corrected.

| | **Currently Depressed** | **Healthy control** | ***p*** |
|---|---|---|---|
| Age (years) | 30.47 (8.29) | 31.2 (8.74) | .70 |
| Male/Female | 12/35 | 9/28 | .90 |
| MÅDRS score | 28.28 (6.03) | 1.3 (1.78) | < .001 |
| YMRS score† | 2.33 (3.0) | - | - |
| HCL score | 19.57 (6.01) | 12.57 (6.97) | < .001 |
| Illness Duration Years (SD) | 9.45 (7.45) | - | - |
| Axis I Diagnosis | Unipolar depression N=39<br>Bipolar Disorder N=7 BP-II N=2 BP-I | - | - |
| Comorbid diagnoses | GAD N=9, SAD N=5, OCD N=4, PD N=2, PTSD N=2 | - | - |

**Table 6-1. Sample characteristics. Values are reported as mean (SD). MÅDRS: Montgomery-Åsberg Depression Rating Scale, YMRS: Young Mania Rating Scale, GAD: Generalized Anxiety Disorder, SAD: Social Anxiety Disorder, OCD: Obsessive Compulsive Disorder, PTSD: Post-Traumatic Stress Disorder. †YMRS scores were recorded only for bipolar disorder subjects.**

## 6.3 Results

Forty-six currently depressed patients and 37 healthy controls, matched on sex, age, and handedness, were recruited. Subjects were diagnosed with either unipolar depression or bipolar disorder (type I or II), and no subjects met criteria for BD-NOS. Demographic and clinical details for both groups are shown in Table 1. HCL scores did not differ significantly between the two scanners used ($t$ = 1.43, $p$ = 0.16).

Support vector regression analysis was able to predict individual bipolarity scores with a mean-squared error of 35.50 (mean absolute error = -4.36); however this was not found to be significant through permutation testing (p = 0.18, permutation test). Furthermore, support vector regression using a polynomial kernel for non-linear modelling did not better represent the relationship between brain structure and bipolarity (p = 30, mean squared error = 35.40, mean absolute error = -4.27).

To test whether this method was successful when trained and tested in healthy controls we performed further exploratory analyses with this group. Support vector regression did not predict bipolarity significantly in healthy subjects (p = 0.83, permutation test, mean squared error = 48.59, mean absolute error = 5.95) and, and similar results were found when using the combined patient and healthy control group (p = 0.42, permutation test, mean squared error = -53.84, mean absolute error = -5.70).

Similarly to the multivariate approach, univariate analyses did not detect any clusters exhibiting significant correlations with HCL scores when using in either the patient or control group.

We also explored relationships between demographic and clinical variables and HCL scores that could potentially affect the interpretation of our results. There was no significant correlation between age and HCL scores ($r(45)$ = .03, $p$ = .86) and HCL scores did not differ significantly between males and females ($t(45)$ = 0.56, $p$ = .58,

$d$ = 0.19). There was also no significant correlation between HCL scores and depression severity, as measured using the MÅDRS ($r(45)$ = .01, $p$ = .95), or between HCL scores and illness duration ($r(45)$ = -.19, $p$ = .20).

## 6.4 Discussion

In the first study to explore brain structural correlates of bipolarity as a dimensional construct within individuals experiencing depressive episodes, we failed to find any evidence that grey matter volume can predict bipolarity as a dimensional trait. This is the first investigation into structural brain correlates of hypomanic symptoms within affective disorders and fails to provide evidence of a structural basis for the concept of bipolarity as a continuum (Angst, 2007).

Our results add to the only previous study which used functional MRI to show that variation in neural systems responsible for affective generation and regulation may be affected by the presence of bipolar symptoms within depressive disorders (Fournier et al., 2013). Hence in the light of our results, we would suggest the neuropathology of bipolarity might only include functional networks. We limited our analysis to regions identified as distinguishing between unipolar and bipolar disorders in our previous meta-analysis (Wise, Radua, Via, et al., 2016), however the results shown here suggest that these differences do not extend to the full range of hypomanic symptoms across mood disorders.

In the healthy control group we also did not demonstrate a significant level of predictive accuracy suggesting that grey matter volume is also not associated with subthreshold hypomanic symptoms in healthy individuals. It is important to mention that the predictive validity of HCL in healthy controls is less clear as the majority of research emphasises the presence of hypomanic symptoms within individuals with

affective disorders (Angst et al., 2011), although there are some suggestions that subsyndromal symptoms of bipolar disorder are present in some healthy individuals (D. J. Smith et al., 2015). However, it is possible that the level and range of hypomanic symptoms in the healthy control group was too limited to successfully identify biological correlates.

In this work participants presented with major depression at the time of scanning and our aim was to predict individuals' levels of hypomanic/manic symptoms within this group using brain regions shown to be associated with bipolarity. For this reason, we focused on regions identified as being associated with bipolarity in a previous comparison of unipolar and bipolar disorders. However, it is important to mention that other discriminative approaches may have advantages in other circumstances. For example, in confirmed unipolar cases it might be more useful to use regions firmly associated with unipolar major depression to potentially test treatment interventions at brain level whereas in case of high-risk individuals with no obvious clinical symptoms it may be more informative to run analyses in regions associated with both depression and bipolarity as a way of potentially predicting susceptibility to either or both conditions.

This study has a number of strengths. Firstly, our sample consisted entirely of individuals free from psychotropic medication. Medications used to treat affective disorders can have effects on grey matter volume (Arnone et al., 2013; Hajek, Cullis, et al., 2012), and our medication-free sample limits the likelihood that such effects are responsible for the null results described here. We excluded individuals who met criteria for substance/alcohol misuse or dependence, further ensuring that our results are not influenced by other psychiatric diagnoses. We also corroborated clinical

diagnoses by reviewing medical notes and by gathering collateral information when available to exclude axis II comorbidity as far as possible.

Another important strength of this study is our use of a machine learning method that offers a number of advantages over traditional univariate voxel-based analysis, including the ability to account for distributed patterns of variation in grey matter volume and to predict bipolarity on an individual basis. Because of this, we are confident that these null results were not due to an inability of traditional univariate statistics to identify more complex patterns of grey matter volume variation that predict bipolarity. Furthermore, our inclusion of traditional univariate statistics that also detected no correlations between grey matter volume and bipolarity suggest that this result is robust to the method used.

However, it should be noted that this study does have a number of limitations. Firstly, we chose to base our feature section on regions shown in previous work to distinguish between unipolar and bipolar disorders. This was based on a hypothesis that these may represent extreme points on a spectrum of bipolarity, and that volume in these regions may therefore vary in line with intermediate levels of bipolarity. However it is possible that although volume in these regions was not predictive of bipolarity, there may be other regions that do accurately predict bipolarity. It is difficult to perform data-driven feature selection with the sample size used here, as defining features on the same data that is used to test predictive accuracy inevitably biases the success of the analysis due to the circular nature of this procedure. In view of this concern, we chose to use a truly independently defined set of features to avoid an inflated false positive rate. Studies using larger samples would be beneficial to enable data-driven feature selection on independent subsets of available data.

Additionally, it is important to note that our sample size was relatively modest, and this may have limited our ability to detect significant predictive regions of volumetric variation. Future research in larger samples may be more successful in this respect. However it is unlikely that this would have led to higher accuracy than detected in cross validation, which typically tends to show exaggerated accuracy (Combrisson & Jerbi, 2015). Furthermore, although we included patients with a wide range of hypomanic symptoms to represent the entire bipolar severity spectrum, including those diagnosed with bipolar I/II disorder, few patients had experienced very severe manic episodes. As a result our coverage of the full bipolar spectrum could be improved. We also included relatively few subjects with very low scores on the HCL, and it may be that the few subjects reporting low scores on the HCL limited the training success of the model at the low end of the spectrum.

Finally, measuring historic bipolar symptoms with self-report measures is open to reporting and recall biases. In the absence of direct observation of psychopathology, the HCL remains nevertheless one of the most reliable self-reported or clinician-rated measures for bipolarity (Angst et al., 2005). Importantly, a high score on the HCL does not necessarily indicate a diagnosis of bipolar disorder and it was not our intention to use the HCL as a diagnostic tool. Nevertheless the HCL has been shown to be sensitive to low-level hypomanic symptoms and to be a clinically meaningful dimension within unipolar depression (Fornaro et al., 2013; Hu et al., 2012; Rybakowski et al., 2012). Our results overall indicate that further research is warranted to evaluate the clinical relevance of the predictive value of high HCL scores at brain level in longitudinal studies. In this context, repeated clinical assessments would be highly valuable not only to confirm affective diagnoses but also reduce potential contamination from axis II disorders which are difficult to fully exclude in studies with a cross sectional design.

Results from this report suggest that structural alterations in the brain are not associated with bipolar symptoms. However, it is likely that there are other systems that may play a role in hypomanic symptoms. There is therefore a clear need for further research into other aspects of other neurobiological parameters that may be associated with bipolarity, such as inflammation (Strawbridge et al., 2015) and fast acting neurotransmission (Arnone, Mumuni, Jauhar, Condon, et al., 2015). Finally, the degree to which such biological parameters can provide prognostic value in terms of stratifying treatment choice and response is an area for future trials.

In conclusion, in this work we were unable to find a pattern of variation in grey matter volume that predicts self-reported bipolarity. This suggests that bipolarity as a dimensional trait does not have a basis in brain structure, and further work is required to examine whether other neurobiological symptoms may demonstrate a stronger relationship with these symptoms.

# 7 Discussion

## 7.1 Summary of findings

### *7.1.1 Aims*

The overall aim of this work was to explore structural and neurochemical alterations in the brain in unipolar and bipolar depression, and understand how these two conditions relate to one another at a neurobiological level. Specifically, I aimed to 1) synthesise the existing literature on structural alterations in affective disorders and compare these between unipolar and bipolar depression to look for overlapping and distinct regions of structural abnormality, 2) explore whether glutamatergic alterations distinguish between unipolar and bipolar depression in a sample without medication, and 3) identify patterns of structural changes that reflect bipolarity as a dimensional construct.

### *7.1.2 Common and distinct patterns of structural alteration*

In two meta-analyses, I showed that unipolar and bipolar disorders are associated with both common and distinct patterns of abnormalities in grey matter volume and white matter integrity. In the meta-analysis of grey matter volume studies, the two conditions were both associated with reduced grey matter volume in the bilateral medial prefrontal cortex and insula, while volumetric reduction in several regions, including the right dorsolateral prefrontal cortex and inferior temporal gyrus, were specific to major depression. In the white matter integrity meta-analysis, a reduction in integrity in the anterior portion of the corpus callosum was common to both disorders, while integrity of the left cingulum was only reduced in bipolar disorder.

Taken together, these results indicate that these two conditions are associated with both common and distinct patterns of structural changes relative to healthy controls, and help to answer the question of whether these disorders might be caused by the same underlying neuropathology. At present, there are few direct comparisons between conditions, and the majority of those that have compared disorders only include relatively small samples (Versace et al., 2010a; Yamada et al., 2015). In view of this, meta-analysis provides an effective way to identify robust and reliable patterns of structural alteration, and the novel meta-analytic methods used here allow valid comparisons between conditions to be made. Notably, there is overlap between the findings of the white matter meta-analysis and a recently published original study comparing corpus callosum integrity between disorders, suggesting that this result is replicable and most likely generalizable across samples (Yamada et al., 2015).

### *7.1.3 Neurochemical alterations*

A further aim of this work was to compare levels of glutamate in the prefrontal cortex of unmedicated individuals with unipolar and bipolar depression. I found that glutamate was similarly reduced in both groups compared to controls, suggesting that reductions in glutamate levels may be associated with a depressive state, as opposed to a distinctive marker for unipolar and bipolar depression as others have suggested (M. J. Taylor, 2014b).

This study has a number of important strengths. Firstly, it is the first to compare glutamate levels between patients with unipolar and bipolar depression during a depressive episode. Previous studies have not directly compared these conditions, and have instead relied on meta-analyses of studies where patients are in different mood states. Studies in unipolar depression tend to use patients who are experiencing a depressive episode, while those in bipolar disorder typically recruit euthymic patients,

and as such it is possible that differences in glutamate levels between conditions may simply reflect an effect of mood state. The findings presented here suggest that this may be the case, as glutamate levels were reduced similarly in both conditions when in the depressed state.

A further strength is that this study included medication free patients. This is notable as it allowed me to look for effects independent from pharmacological manipulation. Unipolar and bipolar depression are often treated with different forms of pharmacotherapy, which could explain apparent neurochemical differences between conditions. The use of an unmedicated sample here avoids this problem, and the results can be interpreted with confidence that they are free from current treatment effects. However, it should be noted that some patients had received previous treatment with medication and psychotherapy, and so we cannot rule out long-term effects of historic treatment.

### *7.1.4 Structural correlates of the bipolar spectrum*

The final aim of this thesis was to explore whether volumetric alterations in the brain reflect bipolarity as a dimensional construct within affective disorders using machine learning. However it was not possible to predict self-reported lifetime hypomanic symptoms, a marker of bipolarity, from grey matter volume with a significant level of accuracy. As such, these results do not support the hypothesis that the bipolar spectrum has a basis in brain structure.

I restricted this analysis to regions identified as showing differences between unipolar and bipolar depression in the meta-analysis of grey matter volume studies, based on the hypothesis that full unipolar and bipolar depression may represent endpoints on a spectrum of bipolarity, and this would be accompanied by variation in the brain

regions associated with the diagnoses. This result suggests however that variation in these areas is not associated with bipolarity as a dimensional construct, and instead represents a substrate of a dichotomous diagnosis.

As with the study on glutamate levels, this study included medication-free, currently depressed patients and so I can be confident that the results are not influenced by medication load or mood state. In addition, due to the multivariate nature of the analyses, I was able to detect spatially distributed patterns of volumetric alteration that traditional univariate methods may not identify, meaning that the null results are not simply due to an inability of the method to detect more complex patterns of variation in grey matter volume.

## 7.2 Methodological considerations

### *7.2.1 Meta-analysis*

Although the method used in the meta-analyses described in this thesis is robust, the very nature of this type of work relies on the quality of the included studies. As such, the results may be affected by weaknesses of the original research studies. An important example of this problem is in the mood states of the patients; the majority of studies including patients with unipolar depression tend to scan patients while in a depressive state, whilst bipolar disorder patients tend to be euthymic. This means that it is difficult to rule out potential effects of mood state on the results. Meta-regressions using depression severity and group comparisons between studies using euthymic and depressed patients were performed to rule out any such effects, although it should be noted that meta-regressions are often limited in power (Thompson & Higgins, 2002). A related concern is the relationship between pharmacotherapy and alterations in

brain structure, as many of the patients included in the original studies were receiving pharmacological treatment.

Furthermore, the thoroughness of the diagnostic procedures in these studies is not always clear. This is particularly important when examining the unipolar-bipolar diagnostic distinction, as individuals with bipolar disorder are often misdiagnosed as unipolar (Angst et al., 2011). This can make it more challenging to identify true differences between disorders if diagnostic labels are not correctly assigned.

It is also not possible from these results to understand what role the observed grey and white matter alterations play in the development of symptoms. In particular, it is not possible to know whether they are causes or consequences of the illness. As an example, there is some evidence that reductions in hippocampal volume may be a result of the illness rather than being a causal factor (Schmaal et al., 2015), although there is also evidence that it may represent a vulnerability factor (U. Rao et al., 2010), and as a result it is important to be careful when interpreting the results demonstrated in this work.

Lastly, the meta-analyses performed here relied largely on reported peak coordinates from included studies, which provide limited information about the true results. Although valid meta-analyses can be performed using this data, the inclusion of the original statistical maps from these studies substantially improves their sensitivity (Radua et al., 2012). A number of these maps were able to be included in the grey matter meta-analysis, which allowed the detection of clusters with smaller effect sizes. Nonetheless, meta-analyses such as these would be vastly improved if original maps were available for all included studies. This was unfortunately infeasible for the meta-analysis of white matter integrity changes due to the time required to obtain statistical maps from authors. The grey matter volume meta-analysis included maps from

previous work, which had been acquired over several years, however such a collection of maps did not exist for white matter integrity.

It is also worth mentioning that approaches other than the voxel-based methods used here provide complementary information in the assessment of volumetric changes in unipolar and bipolar depression. Most notably, the ENIGMA consortium has reported results from large scale meta-analyses of volumetric measures of cortical and subcortical brain regions. This approach involves measurement of the volume of pre-defined regions using Freesurfer, providing a single value for each region which can be compared between disorders.

### *7.2.2 Measurement of hypomanic symptoms*

In chapter 6, I was not able to accurately predict hypomanic symptoms from grey matter volume. However, one important limitation of this study, which may affect offer a potential explanation for this null result, is the reliance on a self-report measure of hypomanic symptoms. This is reliant on patients' memories of symptoms, which may not be accurate, especially with low-level symptoms that are not particularly noticeable for the individual and/or open to recall bias. Issues such as this are difficult to remedy with ease.

Additionally, the HCL (Angst et al., 2005; Feng et al., 2016), the measure of hypomanic symptoms used, does not account for duration of symptoms and may therefore not be indexing some aspects of the severity of these symptoms. This is also difficult to measure accurately using retrospective self-report measures, as patients often do not remember how long certain periods of elevated mood have lasted. One alternative to the self-report questionnaire method may be to use an experience-

sampling method to record hypomanic symptoms over the course of a longer period of time. This could provide a more accurate measure of the levels of these symptoms as less reliant on memory although requiring protracted evaluation which subject to other forms of bias and dropouts.

### *7.2.3 Clinical samples*

The samples used in the analyses presented here improve on those used in previous studies in a number of ways, most importantly by being both currently depressed and not receiving treatment at the time of scanning. However there are also some limitations to these samples. Firstly, the fact that many patients did not have comorbid diagnoses limits our ability to generalise to the many individuals with these disorders who do have comorbid psychiatric disorders. Although the exclusion of comorbidities allows greater certainty that the observed results are truly associated with the conditions of interest, neuropathological mechanisms of disease may be different in patients with comorbid diagnoses.

This is an important issue, and the results here should ideally be complemented by future research examining the role of comorbidity. One particularly common comorbidity in both unipolar and bipolar depression is anxiety. As the samples included in the original investigations reported here were largely free from comorbid anxiety disorders, they are therefore a relatively unrepresentative sample. On the other hand, we can be confident that the results presented here are not an effect of anxiety. It would be interesting for future research to also include comorbid groups to assess whether the abnormalities shown here are also present in those with comorbid anxiety, who represent the majority of cases of depression.

Additionally, the majority of included patients were relatively young and most were female, which again limits the applicability of these results to other populations. This may be a result of the recruitment method used here, focused on online advertisements, which may result in greater exposure to younger individuals (Wise, Arnone, Marwood, et al., 2016a). Nonetheless, the age of the sample does mean that patients had experienced a relatively low number of mood episodes, limiting the likelihood that the results are "scars" of long terms effects from the illness.

### *7.2.4 Magnetic resonance spectroscopy*

Neurochemical changes in unipolar and bipolar depression were measured using magnetic resonance spectroscopy, which provides a simple and accurate method of measuring glutamate levels *in vivo*. However there are some limitations to this method that should be noted. Perhaps most prominently, MRS is unable to spatially map glutamate levels making it difficult to observe spatially distinct alterations in neurochemical levels. This is important as the results presented here suggest that glutamate alterations associated with depression are most prominent in a dorsal area of the anterior cingulate cortex rather than the pregenual region that many studies examine. New methods are in development that allow glutamate to be spatially mapped and compared between groups in a voxelwise manner (Cai et al., 2013), and the application of methods like this to unipolar and bipolar depression could provide clearer insight into the precise location of glutamatergic abnormalities.

Furthermore, it is known that glutamate levels change in response to task demands (Apšvalka et al., 2015), and recent research has demonstrated alterations in glutamatergic responses to tasks in unipolar depression (R. Taylor et al., 2015). Our assessment of glutamate levels at rest may therefore provide an incomplete picture of

alterations in glutamatergic function, and it is possible that unipolar and bipolar disorders might display diversified glutamatergic responses to tasks.

## 7.3 Implications for models of affective disorders

### *7.3.1 Common substrates of depression with unipolar and bipolar disorders*

The work presented here suggests that unipolar and bipolar disorders share a biological basis in the brain to a large degree. It is possible that the common substrates identified reflect commonalities in the symptomatology of the disorders. For example, both conditions are associated with depressive states and impaired emotion regulation, and we have identified alterations in regions involved in affect generation and regulation such as the insula and medial prefrontal cortex, as well as the white matter tracts connecting the two hemispheres of the prefrontal cortex.

Existing models of affective disorders suggest that emotional dysregulation arises due to abnormalities in prefrontal-subcortical systems responsible for these processes (M. L. Phillips et al., 2008; Mary L Phillips & Swartz, 2014; Price & Drevets, 2009); however, to date these have not clearly indicated differences between unipolar and bipolar disorders, and have largely proposed similar underpinnings for both conditions.

The findings of this thesis support these models to a substantial degree. Both meta-analyses demonstrated that prefrontal abnormalities were common to both disorders, suggesting that structural alterations in these areas, which are crucial for emotion regulation, are important in both conditions. However our results extend and complete these models further. Firstly, it is clear from the meta-analysis of grey matter volume that the insula is affected in both conditions. Interestingly this region is typically not a

focus of existing models, which instead centres on prefrontal and subcortical regions. The insula is a large cortical area that serves a number of functions, however it has been particularly associated with awareness of bodily states and has been proposed to be crucial in the experience of anxiety through its role in monitoring bodily arousal (Singer, Critchley, & Preuschoff, 2009). Notably, volumetric reduction in the insula has also been reported in anxiety disorders (Goodkind et al., 2015), albeit in a more anterior region to that shown here, and morphometric reduction in this region may not be exclusive to affective disorders.

Secondly, this work implicates glutamate as marker of the depressive state for the first time in a specific prefrontal network implicated in glutamatergic function, and this suggests that the functional abnormalities in the prefrontal-subcortical emotion regulation systems that these models focus on (Mary L Phillips & Swartz, 2014) may be a result of impaired glutamatergic neurotransmission. This proposal requires direct testing and comparison with other mood states, but if confirmed would provide a plausible neurochemical basis for impairments in emotion regulation. There is some limited evidence that prefrontal glutamate modulates medial prefrontal functional activity during emotional tasks (Stan et al., 2014) and functional connectivity between the medial prefrontal cortex and subcortical regions including the nucleus accumbens and periaqueductal grey area (Duncan et al., 2013), indicating that it can modulate connectivity between the prefrontal cortex and regions involved in emotional processing. Further work investigating whether glutamatergic dysfunction is associated with impaired prefrontal-subcortical function during emotion regulation could provide a strong neurochemical basis for functional the impairments proposed in models of affective disorders.

*A neurobiological model of bipolarity*

Perhaps most importantly, this work identifies a number of neurobiological alterations that distinguish between unipolar and bipolar disorders, an area that current models of affective disorders do not account for. Based on these results, a preliminary model can be proposed to account for differences in symptoms between disorders and inform future research in this area.

The work presented here demonstrates that a number of regions exhibit differential patterns of grey matter volume reduction in unipolar and bipolar disorders. The most notable regions in this respect were the right dorsolateral prefrontal cortex and inferior temporal gyrus. Lateral prefrontal regions have been linked to regulation of emotion (Mak, Hu, Zhang, Xiao, & Lee, 2009; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008), and altered structure in this region may be linked to impairments in affective regulation. Future research could investigate whether this may be linked to the presence of symptoms through an inability to regulate emotion.

Additionally, these findings could allow the development of models that go beyond affective symptoms, and provide an explanation for the cognitive symptoms of these disorders. The inferior temporal gyrus, another region where greater reductions were observed in unipolar depression, is involved in visual working memory (Ranganath, Cohen, Dam, & D'Esposito, 2004). The implications of this area of volume reduction are unclear however, as there is no research into differences in visual working memory between disorders. It will be important for future work to understand whether these observed alterations are truly linked to key symptoms of the disorders.

Additionally, the results of the white matter meta-analysis indicate that there are differences in white matter microstructure that might account for symptomatic differences between conditions. For example, the cingulum has been linked to neurocognitive ability (Delano-Wood et al., 2012), and the reduction in integrity in

this region in bipolar disorder may reflect differences in cognitive profiles between disorders. These conclusions are speculative as this work did not directly link alterations in brain structure to these symptoms. Future research should focus on assessing the potential contributions of these alterations in brain structure to cognitive impairment in bipolar disorder.

However, the findings presented here on volumetric correlates of bipolarity are challenging for the development of comprehensive neurobiologically grounded models of the bipolar spectrum. Numerous studies have reported that hypomanic symptoms are present to a substantial degree in many of those with unipolar depression (Angst et al., 2011; Cassano et al., 2004), indicating that bipolarity may be better represented as a dimensional construct than a binary diagnostic category. However, thus far there has been almost no evidence of a biological basis for this proposed bipolar spectrum, with the literature consisting of one study looking at functional correlates of bipolarity during an emotion processing task (Fournier et al., 2013) and one study of resting state activity (Yang et al., 2016). The work presented in this thesis does not contradict the idea put forward by these papers that bipolarity may have a basis in the brain, but suggests that brain structure may not play as significant a role as brain function.

This also raises the question of whether other neurobiological alterations identified as showing differences between unipolar and bipolar disorders may simply be endpoints of a spectrum, and could in fact also reflect bipolarity as a continuum. For example, it is possible that white matter integrity in the cingulum, identified as distinguishing between disorders in the meta-analysis of white matter studies here, could also correlate with bipolar symptoms as a dimensional construct.

## 7.4 Clinical implications

In recent years, many studies have discussed the possibility of using neuroimaging-based biomarkers to aid clinical decision making (Wise et al., 2014). Although such methods are far from ready for clinical use in their current state, the work presented here suggests that volumetric alterations and changes in white matter integrity can distinguish between unipolar and bipolar disorders, making these an interesting target for biomarker development.

In contrast, despite previous work suggesting that glutamate may distinguish between these disorders, the results presented here indicate that reductions in glutamate levels may instead simply reflect depression as a state, and would therefore not be clinically useful in distinguishing between unipolar and bipolar depression. However, these findings may explain the clinical efficacy of ketamine in both unipolar and bipolar depression if there is in fact a common glutamatergic abnormality in the depressive state.

## 7.5 Future directions

### *7.5.1 Relationship to brain function and symptoms*

This work has identified a number of structural and neurochemical alterations in affective disorders, and sought to identify changes that might differentiate unipolar and bipolar disorders. However a major unanswered question in this area is how exactly these alterations relate to changes in brain functions, and ultimately in symptoms. At present, we are limited to speculating about how altered structure might relate to symptoms such as impaired emotion regulation and neurocognitive ability. Models of affective disorders typically assume that reductions in volume and connectivity will lead to impaired function in emotion regulation networks, and

affective symptoms will arise as a result (M. L. Phillips et al., 2008; Price & Drevets, 2009); however, this assumption may not be correct.

A major task for future research will therefore be to link alterations in brain structure and neurochemical makeup to brain function in affective disorders. This will be a complex task, given that the relationship between structure and function is not necessarily straightforward (Honey, Thivierge, & Sporns, 2010). More complex methods looking at whole-brain structure and connectivity may be required to produce an accurate representation of how the two interact (Tavor et al., 2016). Importantly, developing a better understanding of how alterations in structure and neurochemistry may help to clarify how neurobiological differences between unipolar and bipolar disorders relate to differences in symptoms between the disorders.

### *7.5.2 Causes of neurobiological abnormalities*

An important unanswered question in this field is what causes alterations in brain structure and neurotransmission, and in particular what leads to differences and similarities between unipolar and bipolar disorders. It is possible that common patterns of structural abnormalities in affective disorders may be caused by common risk factors such as early life stress or genetic influences. Previous studies have linked childhood trauma, a risk factor for both conditions (Garno, Goldberg, Ramirez, & Ritzler, 2005; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008), to reductions in grey matter volume (U. Rao et al., 2010; Vythilingam et al., 2002). Notably, one study reported reductions in medial prefrontal volume in individuals reporting a history of childhood trauma (van Harmelen et al., 2010), albeit in a more dorsal location than the areas identified here as showing common reductions in both unipolar and bipolar disorders. Similarly, both conditions share similar genetic risk alleles (Consortium, 2013), and given the known genetic influences on brain volume (Hibar et al., 2015)

it is possible that shared genetic risk in these conditions underlies the shared volumetric alterations. Future research is required to directly test these hypotheses, and also to identify causal factors that can explain distinct patterns of neurobiological changes in these conditions.

### *7.5.3 The role of glutamate in depression*

The research reported here on glutamatergic dysfunction suggests that reductions in glutamate levels are a marker of the depressive state rather than being a marker of bipolarity during this state. However, further studies directly comparing patients in depressed and euthymic states, ideally using longitudinal methods within subjects, to confirm whether glutamate levels do indeed fluctuate depending on mood state. Additional non-clinical work could use new developments in MRS, such as functional MRS, to test whether glutamate levels reflect short term fluctuations in mood, and this would provide a more direct link between glutamatergic changes and mood state.

Pharmacological manipulations of glutamatergic neurotransmission using ketamine appear to have a rapid antidepressant effect, suggesting that glutamate may indeed be involved in mood (Krystal, Sanacora, & Duman, 2013). Ketamine leads to a rapid increase in prefrontal glutamate levels, as measured by MRS (Stone et al., 2012); however, the pathways underlying this antidepressant effects are unclear, and it is likely to be mediated by more complex mechanisms than a simple increase in glutamate levels (Browne & Lucki, 2013). Developing a clearer understanding the antidepressant effects of glutamatergic drugs could provide insights into the relationship between alterations in glutamate levels and affective symptoms.

### *7.5.4 Neurobiological correlates of bipolarity*

As mentioned previously, another important task for future research will be to identify further neurobiological systems underlying the bipolar spectrum, and build comprehensive theoretical models based on this data. Practically, this is not a challenging aim as bipolar symptoms can be measured easily using brief self-report measures, which can be added to any study on major depression. However, going beyond simple correlational analyses with self-report measures will be more difficult. One way to establish causality in this respect may be to compare regions of grey matter change that correlate with bipolarity to regions identified as being associated with hypomanic symptoms in lesion studies. Another way might be to design longitudinal studies whereby identified patients can be followed up for a number of years and scanned at different time points and mood states. Additionally, if convincing animal models of hypomanic symptoms are developed, these could provide insights into the neurobiological basis of bipolarity as a distinct symptom from depression.

### *7.5.5 Conclusions*

This work aimed to identify common and distinct patterns of structural and neurochemical alteration in unipolar and bipolar depression, and to examine whether bipolarity as a dimensional characteristic was represented at a biological level. The results presented here indicate that while these disorders share largely overlapping pathology, there are also some important distinctions between disorders, particularly in white and grey matter. However, alterations in grey matter volume did not predict bipolarity as a dimensional trait. Together, this work suggests that affective disorders share common patterns of pathology that relate to the depressive state, and that differences between disorders are more closely related to categorical diagnoses than to bipolarity as a dimensional construct.

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# 8 Appendix 1 – Contributions to the work presented in this thesis

Chapter 1: I wrote all parts of this chapter, with guidance from Dr Danilo Arnone and Prof Tony Cleare.

Chapter 2: I wrote all parts of this chapter, with guidance from Dr Danilo Arnone and Prof Tony Cleare.

Chapter 3: I conducted literature searches and performed statistical analyses for this chapter. The chapter was written by myself with assistance from Dr Danilo Arnone and was reviewed by all named authors of the published paper, as well as anonymous reviewers.

Chapter 4: I conducted literature searches and performed statistical analyses for this chapter. The chapter was written by myself with assistance from Dr Danilo Arnone and was reviewed by all named authors of the published paper, as well as anonymous reviewers.

Chapter 5: I collected all described in this chapter with assistance from Dr Danilo Arnone and Dr Andres Herane-Vives. I performed all data processing and analysis with assistance from Dr Matthew Taylor. The chapter was written by myself with assistance from Dr Danilo Arnone and was reviewed Dr Matthew Taylor, Dr Andres Herane-Vives, Dr Antonella Marion Gammazza, Prof Francesco Capello, Dr David Lythgoe, Prof Steve Williams, Prof Allan Young and Prof Tony Cleare.

Chapter 6: I collected all data used in this chapter with the assistance of Dr Andres Herane-Vives and Dr Danilo Arnone, except for the additional structural sample for which data was collected by Lindsey Marwood. I wrote the chapter with assistance

from Dr Danilo Arnone and Prof Tony Cleare, and it was reviewed by Lindsey Marwood, Dr Adam Perkins, Dr Andres Herane-Vives, Prof Steve Williams and Prof Allan Young.

Chapter 7: I wrote all parts of this chapter, with guidance from Dr Danilo Arnone and Prof Tony Cleare.